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THE CLINICAL LABORATORY AS AN AID TO SURGERY

A SYMPOSIUM

(Concluded from April issue)

FORTY YEARS AS A CLINICAL PATHOLOGIST*

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FOR forty years I have been actively interested in diagnostic pathology. In 1891, with George Dock, the foundation was laid at Ann Arbor for a scientific department of Internal Medicine. Dock's interest was fundamentally pathologic, and very naturally our approach to internal medicine was through pathology. With the small amount of clinical material then available, we had time and opportunity to do practical work in pathology in our embryonic laboratory of internal medicine. At that time no diagnostic pathology was being carried out at Michigan; the only pathology given to students was a crude course, chiefly histologic, of thick sections cut with a razor on an ice-and-salt freezing microtome, and stained with log wood, usually so black that no details could be recognized. The then Professor of Pathology was a Britisher, lately retired from the command of a gunboat, chasing pirates in the China Sea, and had been picked up in London and brought to Ann Arbor by one of the members of the medical faculty. He was thoroughly a picturesque character, and had really made some interesting histologic observations; but he knew nothing of pathology, and spent his time attempting to demonstrate that the tubercle bacillus was not the cause, but the result of tuberculosis. Dr. Dock's training in diagnostic pathology had been both scientific and practical; so rather sub rosa we carried on diagnostic pathology as the foundation stone of internal medicine. We examined the surgical material taken from our patients, did our own autopsies and ran them through; and gradually an increasing amount of material was sent

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in for diagnosis. I spent the summers of 1893-4-5 in intensive pathologic study in Vienna; and in the fall of 1895, it fell to me to succeed the Chinese pirate-chaser as the practical head of the Department of Pathology in the Medical School. Dr. Dock, nominally the head, gave me absolute freedom to organize and carry on the department according to my own ideas and desires. He never interfered, practically never suggested, and always backed me up. For this wonderful opportunity I have always been grateful, and I take the opportunity of acknowledging my indebtedness to him here.

The first foundation stone of my department consisted in getting the Board of Regents to pass a rule requiring that all surgical material removed in the University Hospitals became the property of the Pathological Laboratory, and must be sent there, accompanied by a history of the case for diagnosis. This included all tissue; tonsils, placentas, herniotomy tissue, and everything else removed at operation. The Departments of Surgery, Gynecology and Obstetrics, and Otolaryngology have in all these years with few exceptions lived up to this rule and have quite fully cooperated in this respect. The results show the great wisdom of such a procedure. Not only has much material regarded as wholly negative by the clinician been shown to have decided pathologic value of great importance to both patient and clinician, but through the years there has grown up a collection of pathologic material that probably has no equal in any other diagnostic laboratory in the world. Slides and records of over 150,000 cases are immediately available for comparative study. Over 50,000 tonsils can be studied, and surely in such a group the complete pathology of the tonsil must be represented; and this has been shown by the contributions to tonsillar pathology coming from this laboratory. The value of the routine examination of the placenta is shown in that over a dozen cases of tuberculosis of the placenta, regarded such a rarity in the literature as to be almost negligible practically, have been reported by us. The same thing is true of syphilis of the cord and placenta, of which many cases exist in our files. Many other things considered rare in the average laboratory can be assembled by the dozen or hundreds of cases from our collection. I may mention only the leucemic and aleucemic conditions, Hodgkin's, mycosis fungoides, metastasizing carcinoid of the appendix, metastasizing giant cell tumor of bone, blastomycosis, hundreds of cases of actinomycosis, and numerous other conditions regarded in the literature as of rare occurrence. It has been possible to make notable contributions to the pathology of syphilis, goiter, and cancer out of this rich material. Particularly is this true of our neoplasm material which contains thousands of cases of the ordinary types of neoplasm, all of the forms described in the textbooks, as well as many of which no exact counterpart apparently exists in the literature. This collection, which has taken a whole lifetime to assemble, could now be utilized for a lifetime of research and study; and my great regret is that not enough years are now available to me for such use of this material.

In my first year as pathologist I was the only active member of the department. I gave all the courses, lecture and laboratory, in pathology, and in addition conducted a one-hour course in internal medicine. All of the

pathologic diagnostic material was blocked, cut and stained, and diagnosed by myself, as well as some 30,000 teaching preparations given out to my students in the laboratory course each year. Each afternoon from 1 to 5 was spent in the demonstration of those sections, and this went on throughout the entire year. Most of the pathologic material used in this course I had obtained in Vienna; but from the very first a special effort was made toward utilizing the local material for purposes of practical illustration. I have always insisted that pathology was a practical subject and that the practical pathologist made the best teacher. Pathology was not to my mind a separate subject to be taught academically, but one underlying and intimately connected with all of the clinical subjects of the curriculum. The teaching pathologist should also be a clinical pathologist. This meant broad and not narrow teaching; it meant a very full and hard course for the average student of those days, hence the resultant bad reputation which my courses came to have among the unintelligent student majority of that period. But student popularity was neither a thing desired nor sought by me, unless it came as an unasked appreciation from my best students. And this it has always been. The correlation of pathology with the living clinical picture represents to my mind the highest function of medical teaching, and were I starting my career again today, I should follow the same ideals and practice initiated in 1895. The method of my teaching followed that of clinical diagnosis. Sections were given out as unknowns, studied and analyzed by the student, and the final diagnosis rounded off by student and teacher together. It was hard teaching, but I do not regret it. On the contrary, I am more than ever convinced that this method is the only true didactic one.

In my first year (1895) as clinical pathologist to the hospital, I had only 158 cases and 12 autopsies, a striking contrast to the 18,194 diagnostic cases and 401 autopsies of the last year. But from the single man of that first year there has developed a departmental staff of 24 members. During my first years of service my contact with the clinicians produced many interesting experiences. Very early I had come to the belief that the giant cell tumor of the epulis type, or giant cell sarcoma as it was then universally called, was a relatively benign neoplasm. In a report to the surgical chief I made the suggestion that such was the case and that thorough local excision rather than amputation was indicated. In wrath he descended upon me to inform me emphatically that the only diagnosis he wanted from my department was that of sarcoma; he would then use his own judgment as to the operation. He lived long enough to see my view of the relative benign character of the giant cell tumor accepted by almost everyone. During my first year there were a number of pus tubes sent to the laboratory on which I returned a diagnosis of "gonococcal pus tubes." This brought a visit from the gynecologist, who rushing into my laboratory shouted, "What do you mean, young man, by saying that these tubes are infected with gonococci? These are all decent, married women." He also lived long enough to accept a gonococcal etiology for the majority of pus tubes. Still more reluctantly were diagnoses of syphilis in operative material received. Often at first they roused active dissent. When cases of gummatous lesions of skin,

bone, and lymph nodes had been clinically demonstrated as neoplasms and operated upon as such, it was but natural that the clinician should object to the returned diagnosis of syphilis. Even after the demonstration of the spirochete had been made possible, this same reluctance to accept a pathologic diagnosis of syphilis persisted for some time. But through the years the clinician has become more and more reconciled to the pathologist and dependent upon him. Many cases are actually referred to the pathologist for his opinion before operation. There is an increasing tendency to advance the pathologist to the position of a consultant. The clinical-pathologic conference has become one of the most popular and appreciated courses of instruction in the Medical School; and the conferences of surgical and pathologic staffs are similarly well attended and participated in by the clinical members.

Differences of standpoint between clinician and pathologist will of course always come up. For many years there existed a constant difference of opinion between surgery and pathology relative to the clinical diagnosis of sarcoma of the breast, which always to the pathologic eye presented the appearances of an intercanalicular adenomyxofibroma. In recent years the clinical diagnosis of sarcoma of the breast has disappeared from our records. In our laboratory the clinical diagnosis of adenomatous prostate has always been offset with the pathologic diagnosis of cystic glandular hyperplasia due to chronic duct-infection. In my forty years of pathologic work I have never but once seen a true adenoma of the prostate. I am convinced that the enlarged prostate is not due to the production of adenomas, but is the result of a cystic glandular hyperplasia following retention of secretions, usually as the result of a chronic duct infection. The richness of our material and the more intensive study accorded it than is usual in diagnostic laboratories, because of its intimate relationship to the teaching and research, are responsible for the very decided opinions that have originated at Michigan. As early as 1893, I was teaching the importance of the constitution and of heredity in disease, at a time when these subjects received scant or no attention in the textbooks. Particularly with reference to the hereditary susceptibility of cancer did the experience of this laboratory antedate general opinion; and my expressed views were bitterly attacked, even by my own colleagues. He, who is convinced and waits patiently, receives in due time his reward. Similar was the situation as regards my early conception of the neoplastic nature of chloroma, the leucemias, lymphoblastoma, myeloma, Hodgkin's, and mycosis fungoides. This fight is still on, as Ewing's Memorial Number of the Annals of Surgery attests, in that an article by me on the neoplastic relationships of these conditions is preceded and followed, that is, surrounded, by articles favoring the tuberculous etiology of Hodgkin's. Again we can afford to wait patiently; the only sad thing about it is that the remaining span of life may be too short for the settlement of this matter. Very early I predicted that the broad tapeworm would become endemic in the Great Lakes region, but was unable to arouse any interest in a palpable situation in the United States bureaus concerned with the study of animal parasites. This prediction has already become true. Among other things for which this laboratory has had to fight for its views, were the tissue-

lesions produced by irradiation, the importance of fat-embolism, the existence of hemolymph nodes in man, the non-entity of the Banti's syndrome, Ayerza's disease, the importance of cardiovascular syphilis, the constitutional foundation of Graves' disease and toxic goiter, the rarity of the relation of gastric ulcer to carcinoma, and other mooted questions. One must of necessity acquire a broad view from experience with such a rich material as that flowing into this laboratory. Gradually one has been convinced that the benign giant-cell neoplasm may rarely take on the characters of malignancy; and that the same thing is true of the carcinoid of the appendix. Both of these neoplasms may sometimes metastasize. Further evidence of the richness of our material may be shown by the fact that from it several hundreds of cases of actinomycosis may be mobilized for study.

The function of the diagnostic laboratory is to serve the clinician to the best of its ability. Hence speed in the return of the diagnosis becomes a chief desideratum. When I assumed charge of this laboratory the few diagnostic cases sent to the previous pathologist required weeks for their diagnosis. At the first this was reduced to one week, the diagnosis being ready for the clinic following that in which the patient had been operated upon. This rule was strictly adhered to, and promptness in returning the diagnosis became a leading criterion of the laboratory. For the first several years all diagnostic material was run in celloidin. By gradually improving the method the time was shortened to two and a half days. About 1900 the paraffin method wholly replaced the celloidin, and the time was shortened to one day. At the present time the following routine method is employed. The material is cut into suitable blocks and put into a 10 per cent formalin solution each day at five o'clock in the afternoon. In this it remains until seven o'clock. The night technician then runs the tissue through three changes of absolute alcohol, blotting on absorbent paper between each change, this process lasting an hour; the blocks are then transferred in the same manner to the first xylol for 15-30 minutes, then blotted, and placed in second xylol for one hour; then in first paraffin (56°) for 30 minutes, then in second paraffin for overnight. At seven in the morning the tissue is blocked in fresh paraffin, cut, stained, and ready for diagnosis at ten o'clock. All diagnoses are typed and sent to the clinician by eleven to twelve o'clock of the morning following the operation. For the great majority of operative cases, this is sufficiently prompt for all purposes. The writer has never been very sympathetic with the rapid-fire frozen-section method of diagnosis so much lauded by certain surgeons. Its universal application in the clinic is only that of a fad or pose. Actually in practice the number of cases requiring the diagnosis while the patient is on the operating table is very small. For these the frozen-section method serves a most useful purpose. But this method as a routine has very marked disadvantages as compared to the rapid overnight paraffin method. In the first place the number of blocks frozen is usually very much less than those blocked in paraffin; serial sections cannot be obtained, and staining methods are limited usually to one which is not permanent. Hence the great importance of preserving slides as records of the case is wholly lost. It is notorious that one of the largest

surgical clinics in the country employing this method can never furnish any slide records of a given case, although extremely solicitous of having such slides sent from other clinics with referred patients.

In the majority of smaller hospitals and clinics using the frozen-section method, usually only one block of tissue is frozen, and the case diagnosed from sections made of the one block. To my mind this method is absolutely dangerous, as experience has taught us that the pathologic condition, particularly a neoplasm, may be limited to a very small area in one block, which may easily be missed if blocks are not made from all parts of the tissue removed. For this reason I have made it a rule in this laboratory that the whole of a prostate must always be examined in 7 to 12 blocks, that the same thing must be carried out in the case of the mammary gland, gall bladder, thyroid, etc. Particularly is it important to examine many blocks in the case of neoplasms of the periosteum or bones, owing to the different degrees of differentiation and entdifferentiation usually shown in different parts of the same tumor. Further, pathologic conditions of the appendix, tubes, etc., are often sharply localized to either the proximal, middle, or distal portions. Hence blocks are routinely taken from all portions of these organs. Still more important is this in examinations of the umbilical cord for syphilis, and of the aorta and myocardium for syphilitic lesions. Tonsils, ovaries, testes, adrenals, etc., are always bisected, and one-half of the organ run through. This thorough examination of the material is not a part of the slap-dash frozen-section method in vogue in most of our clinics.

Further, the staining technic employed in most of our laboratories using the frozen-section method is, to my mind, absolutely inexcusable and positively criminal. Hundreds of sections, so prepared, are referred to me yearly for diagnosis from all over the country. How often has it been necessary for me to return the slide with the statement, "No diagnosis possible because of poor technic!" It makes one shudder to think of the kind of diagnosis from impossible slides going on all over the country. No training is more difficult and far-reaching than that of a competent diagnostic pathologist, yet hospitals and clinics are content in many cases to have this most important work carried out by interns, orderlies, inexperienced assistants, and even women laboratory technicians. From one diagnostic clinic there were sent to me during two years, five slides of five different cases of curettings from young women, on each of which a diagnosis of adenocarcinoma had been made. Because of the youth of their patients the clinicians had objected to the diagnosis of carcinoma. In each case the slides showed only a decidual endometrium; abortion rather than carcinoma was the proper diagnosis. It is possible to make beautiful preparations by the frozen-section method, as for example, those of MacCarty at The Mayo Clinic; but few laboratories employing this method achieve similar results. The freezing method has a very definite but limited sphere of usefulness, and according to my opinion should not be used as a routine diagnostic method. Too much is sacrificed.

The use of the combined celloidin-paraffin method by means of the molasses plate, as devised in our laboratory, has been to us one of the greatest time-savers, and has made possible the expedient management of our large

material. By this means our sections are stained as one in celloidin sheets of fifty to seventy sections or more, then cut and mounted separately. The details of this method are easily mastered by our technical assistants, and, with the use of the appliances originating in the laboratory, are quickly and most efficiently carried out. A certain grade of technical excellence is constantly required, so that as far as technic is concerned, we get all from the material that can be obtained from it. For spirochete staining, the laboratory has a special assistant specializing in this technic. This is probably the only laboratory in the country in which routine spirochete staining is carried out. This has been made possible by the development of our silver-agar staining methods applicable to the staining of single sections on cover-glasses.

The most unsatisfactory side of the work of a diagnostic laboratory is still today our inability to get a properly filled-out history sheet sent to the laboratory with the specimen. Aside from the bare facts necessary to a proper record, there are certain matters of information of great importance in the formulation of a diagnosis that will be of the greatest service to both surgeon and patient. Moreover, certain facts of deepest scientific interest should be stated in the record to be utilized for later study and investigation. Since 1895, I have struggled to have the family incidence of neoplasm investigated in the case of every patient having a newgrowth; yet less than 1 per cent of our histories previous to 1910 gave any family history of the incidence of neoplasm at all. An investigation of those same cases by means of special letters or personal communications with the families of those patients raised the percentage of this incidence to over fifty. Even in a specialized teaching hospital such as ours, it is still very difficult to get adequate and satisfactory histories of the pathologic material coming from some of the clinics. History taking is still one of the branches of instruction in the hospitals of this country most neglected and most poorly taught.

Just one word concerning the grading of malignancy of neoplasms. A certain amount of danger is inherent in some of the recent pronouncements relative to this question. While the general principles of variation in malignancy according to the degree of difference in differentiation and entdifferentiation have long been recognized by the diagnostic pathologist and used by him as criteria for prognosis, it must be emphasized here that all degrees of anaplasia may be found in a single neoplasm, in fact, are found in the majority, so that one's grading of malignancy will vary in the case of the same neoplasm according to the part of the neoplasm from which the piece examined is taken. Particularly is this fact of great importance in the case of bone tumors. Such may show only the appearances of osteoma, chondroma, or fibroma in large areas; while in relatively small and circumscribed areas will be found the cellular and atypical tissue that stamps the growth as an osteogenic sarcoma. In one case of neoplasm of the tibia, material was distributed to four pathologists; one made a diagnosis of fibroma, another of chondroma, the third of osteoma; while the fourth who happened to be myself, received a piece showing atypical cellular areas justifying the diagnosis of osteogenic sarcoma, which diagnosis was later proved to be correct. Many carcinomas, particularly those of the thyroid and lungs, present the most

varying pictures of anaplasia in different portions, so that sections from these different areas would be regarded as entirely distinct and different neoplasms, were the origin of the material not known. The most common form of carcinoma of the breast is always scirrhous in its older portions, and medullary in the most recent. Therefore, the broad view is necessary in the making up of any pronouncement as to the degree of malignancy of any given neoplasm. Numerous blocks should be examined, and the general relations weighed, rather than any consideration of the character of cells taken at chance from any portion of the neoplasm. Further, it may be urged that the degree of anaplasia is in itself no positive guide for the degree of malignancy. Every diagnostic pathologist has seen neoplasms showing but little, or no apparent, departure from the normal type of cells, but still infiltrating and metastasizing after the manner of the most malignant types. Many of the present-day laboratory attempted gradings of neoplasms are based upon false principles, and are dangerous. Again I will insist that the broader the view respecting neoplasms, the safer will be the pathologist's judgment as to prognosis. Each case must be considered according to its own individual characteristics. The family history is an important factor in determining the prognosis. In my experience we have found a marked tendency for malignancy to occur earlier and to be more marked in degree in individuals from families showing a multiple incidence of malignancy in different generations than in individuals with family histories free from such multiple incidence.

In this somewhat rambling paper I have touched briefly upon a number of points that stand out as significant in my long experience as a practical diagnostic pathologist, in the hope that they may have some value or interest to a younger generation. Methods and details may change, but the essential principles underlying a successful career in diagnostic pathology will not. I cannot close, however, without some expression of the joy of life that I have found in my practical diagnostic work. In spite of its mass, and the inevitable recurring appendices, cystic ovaries, cervical erosions, etc., a routine that others complain of as tiresome, no day in this work has been without its thrill. Something wholly new, or new aspects of old things, constantly turn up in the material, and each day on finishing my trays of diagnostic slides, I arise mentally stimulated, and never tired. It is this constant meeting with the unexpected that gives zest to the life of the diagnostic pathologist and keeps his mind fresh and receptive. The joy of the pursuit is his always. I can wish no one any greater happiness in life than that possible to the practicing pathologic diagnostician with a large and varied material in his service.

CHEMICAL ANALYSIS OF BLOOD IN GENERAL AND UROLOGIC SURGERY*

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ALTHOUGH the chemical analysis of blood appears to have first found clinical application in internal medicine, its usefulness in surgery was not long in gaining recognition, particularly in urologic surgery. There are now a rather large number of conditions which demand the preoperative prognostic information which may be furnished by a chemical analysis of the blood. It is the aim of the present paper to briefly summarize such information.

Since two of the most important functions of the blood are to carry nutritive elements to the various tissues and waste products to the organs of excretion, it is evident that faulty metabolism or elimination should be detected by a chemical analysis of the blood. For example, in diabetes there is a rise in the blood sugar, while an elevation of the nitrogenous waste products occurs in certain renal disorders. The surgeon very frequently has to contend with conditions of acidosis and alkalosis, which, if not properly evaluated and treated may lead to death. There is no method of measuring the acid-base equilibrium of the body comparable in accuracy to the chemical analysis of the blood.

In Table I are presented the various blood determinations which have been found most useful from a clinical point of view. The table includes the range of normal findings, figures which may be considered the beginning of the pathologic, and the pathologic range of variations.

Hemoglobin.—The estimation of hemoglobin may be made so readily on a chemical blood specimen that it ought to be included in every chemical blood examination. Most of the older clinical methods take 100 as the normal, this being equivalent all the way from the 13.77 gm. used in the Dare method to the 17.2 gm. per 100 c.c. employed in the Sahli method. Since the normals for men, women, and children are different, it is much more logical to record the observations in grams hemoglobin per 100 c.c. of blood, as has been done in Table I.

Nitrogenous Waste Products.—Interest centers in the three nitrogenous waste products, urea, creatinine, and uric acid. Since the *urea nitrogen* normally forms about half of the nonprotein nitrogen and since with nitrogen retention the proportion increases, the two determinations tell essentially the same story. Of the two determinations the urea nitrogen is probably to be

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Most of the topics discussed in this paper are presented in greater detail and methods given in Myers, V. C.: Practical Chemical Analysis of Blood, The C. V. Mosby Co., St. Louis, 1924. A new edition is in preparation.

TABLE I

CLINICALLY SIGNIFICANT CHEMICAL BLOOD CONSTITUENTS

CONSTITUENT OR DETERMINATION	NORMAL RANGE	BEGINNING PATHOLOGIC RANGE	PATHOLOGIC RANGE
	Per 100 c.c.	Per 100 c.c.	Per 100 c.c.
Hemoglobin	14-17 gm.	- 12	3- 23
Nonprotein nitrogen	25-35 mg.	+ 35	20-400
Urea nitrogen	12-15 mg.	+ 20	5-350
Creatinine	1- 2 mg.	+ 3.5	to 34
Uric acid	1-3.5 mg.	+ 4	to 27
Blood sugar	70-120 mg.	+150	40-1,300
Diastatic activity (Myers and Killian)	15-20%	+ 25	
Cholesterol	140-170 mg.	-130	60-1,000
Carbon dioxide capacity	50-70 vol. per cent	- 45 + 70	5-130
Chlorides as NaCl			
Plasma	570-620 mg.	-500	300-850
Whole blood	450-520 mg.	-450	120-700
Calcium as Ca	9-11 mg.	- 8	3- 20
Inorganic phosphorus as P			
Adults	2.5-4 mg.		2- 40
Children	4-6 mg.	- 4	
Icteric index	4-6 terms 1:10,000 $K_2Cr_2O_7$	+ 10	10-225

preferred, although the nonprotein nitrogen is an excellent check on the urea. Urea is the chief end-product of nitrogenous metabolism, and its excretion is one of the kidney's most important functions. Since the kidney normally eliminates urea very completely (down to from 12 to 15 mg. of urea nitrogen per 100 c.c. of blood) its rise in the blood constitutes a most reliable index of the impairment in renal function. Urea is normally in large part exogenous in origin, and improvement as a result of such therapeutic measures as diet, urinary drainage and rest is beautifully shown by the fall in the blood urea. The estimation of the blood urea is important in all forms of nephritis, and in intestinal obstruction. It is probably the most valuable preoperative prognostic test in conditions with urinary obstruction, such as prostatic obstruction, bladder tumor, and calculi in various parts of the urinary tract. Although it does not differentiate between the two kidneys, it does tell whether one of them is functioning satisfactorily.

The question may naturally be raised as to the comparative value of the blood urea nitrogen and the phenolsulphonephthalein test. The phenolsulphonephthalein test nicely supplements the blood urea, and appears to furnish reliable information in cases without urinary obstruction and without edema. With urinary obstruction, the patient must be very carefully catheterized or the phenolsulphonephthalein test is not only useless but misleading. With cases suffering from edema, such as occurs in nephrosis, the phenolsulphonephthalein output when administered intramuscularly is very poor, probably due to slow absorption of the dye, and does not give results comparable with the blood urea.

Likewise, if one is to employ the *urea clearance test of Van Slyke*, the necessity of accurate catheterization in cases with urinary obstruction cannot be overemphasized. The factor of safety as regards the kidneys is quite

large and their functional activity must be reduced to considerably less than half the normal before an elevation in the blood urea occurs. Van Slyke and his coworkers[1] consider that in the early recognition of impaired renal function the "urea clearance test" is distinctly superior to the blood urea alone, since the test will show an impairment in renal function before an elevation of the blood urea occurs. However, it would appear from a surgical point of view that a patient with a blood urea nitrogen below 20 mg. was a good risk so far as the kidneys were concerned.

The estimation of *creatinine* is indicated only in conditions of nitrogen retention in which the urea nitrogen is above 20 mg. Here the creatinine may furnish more reliable prognostic information than the urea. Creatinine figures of 5 mg. and above[2] constitute a very unfavorable prognostic sign, unless, as rarely happens, the retention is due to some acute cause.

Retention of *uric acid* occurs in so many different conditions that its elevation is of rather less significance than urea and creatinine. Its elevation in gout is well known and may serve to differentiate gout from infectious arthritis. In nephritis, uric acid appears to be retained earlier than urea, but it should be borne in mind that high values for uric acid are found in eclampsia, starvation, arterial hypertension, lead poisoning, and acute infections, especially pneumonia.

Blood Sugar.—Until very recently figures for the normal blood sugar were considered to vary from 90 to 120 mg., but we now know that these figures are too high by rather more than 20 mg., since nonsugar reducing substances interfere to this extent with most of the older methods, including the popular Folin-Wu method. A blood sugar of 150 mg. or above with the older methods may be considered definitely abnormal.

The estimation of blood sugar finds its chief use in the modern management of the diabetic patient. However, the determination is necessary for the diagnosis of renal diabetes, and moderate hyperglycemias are frequently found in nephritis, hyperthyroidism, pancreatic disease and some infections, while hypoglycemias are encountered in hypofunction of the thyroid, adrenal and pituitary, and after too large an administration of insulin.

The *diastatic activity* of the blood is found to be increased in practically all conditions showing hyperglycemia, and appears to stand in somewhat of a causal relation to it. High figures are encountered in diabetes, nephritis, hyperthyroidism, pancreatitis and other conditions affecting the pancreas. It appears to possess some diagnostic significance in pancreatic disease.

Cholesterol.—Although the cholesterol content of the blood varies in a number of pathologic conditions, most of these are of relatively little diagnostic value. However, the high concentrations found in nephrosis are almost pathognomonic. In diabetes the cholesterol content quite closely parallels the lipemia. It is also increased in obstructive jaundice, pregnancy, and in some, but not in all, cases of *cholelithiasis*, but decreased in pernicious anemia.

Acid-Base Balance.—One of the most valuable chemical blood determinations in both medical and surgical cases is the Van Slyke CO_2 capacity (or combining power) test, since with its aid one can measure the alkaline reserve and obtain a fair idea of the state of the acid-base balance. With

figures for CO_2 above 35 and below 70 per cent by volume, the CO_2 alone furnishes a quite reliable index of an acidosis or alkalosis, but with figures outside these limits, the acidosis or alkalosis is probably uncompensated; i.e., the reaction (P_H) of the blood is abnormal. Here it may be necessary to determine the P_H to obtain a correct appraisal of the acid-base balance. The P_H of the blood is a function of the ratio $\frac{HNaCO_3}{H_2CO_3} = \frac{19}{1}$. Obviously, anything which will lower the numerator or raise the denominator, will produce an acidosis, while converse changes will result in an alkalosis. The bicarbonate buffer system is in equilibrium with a number of other buffer systems, the most important of which is the hemoglobin. Any change in the bicarbonate will therefore affect all the other buffer systems, and vice versa. Since $HNaCO_3$ will combine with any acid to form a salt, and CO_2 and H_2O, it has been referred to as the first line of defense against acidosis.

Determinations of the CO_2 capacity should be a routine preoperative test on all patients who are seriously ill, since the CO_2 may fall from 10 to 20 per cent by volume as the result of an operation in which a general anesthetic (ether) is used. As insulin is a specific for diabetic coma, a surgical operation on a diabetic patient is no longer attended with unusual danger.

Chlorides.—With the rise in the plasma bicarbonate which occurs in intestinal obstruction there is a corresponding fall in the plasma chloride. As pointed out by Haden and Orr,[3, 4] the replacement of this plasma chloride is of great therapeutic value. This fall in plasma chloride occurs to a less marked extent following the rise in plasma bicarbonate which takes place after large doses of sodium bicarbonate. The plasma chloride may be much reduced in mercuric chloride poisoning and pneumonia. In nephrosis, despite the marked edema, the chloride concentration is essentially normal. However, high figures for the plasma chloride are found in some cases of nephritis and eclampsia.

Calcium and Inorganic Phosphorus.—The serum *calcium* is lowered in infantile and parathyroid tetany, the tetany being a consequence of the reduction in the calcium. It is also lowered in the terminal stages of nephritis, although here tetany does not often occur owing to the presence of acidosis. The *inorganic phosphorus* of the blood is lowered in rickets, while cases of fractures with nonunion are apparently due to lack of mobilization of phosphorus and calcium. In the terminal stages of nephritis the inorganic phosphorus may be elevated to a marked degree, furnishing a very unfavorable prognosis.

Icteric Index.—The icteric index is a simple and relatively accurate method of measuring the bilirubin of the blood serum, if one excepts an occasional case of carotinemia. It is a very useful functional liver test in clinical work, since it helps in the diagnosis of cases of cholecystitis and cholelithiasis without clinical jaundice; is an aid in distinguishing between obstructive jaundice due to malignancy and catarrhal jaundice by showing whether the jaundice is increasing, diminishing or stationary; serves as an excellent guide to the tolerance of the liver to arsenicals in the treatment of syphilis; is helpful in the diagnosis of cirrhosis and malignant metastases in the liver,

and determines whether obstructive jaundice has been relieved by operation. It helps to differentiate primary and secondary anemia. The van den Bergh reaction gives added information in some cases, since it supposedly differentiates between the obstructive and nonobstructive forms of jaundice.

TABLE II

CHEMICAL BLOOD DETERMINATIONS INDICATED IN SURGERY AND G. U. SURGERY

CONDITIONS	DETERMINATIONS INDICATED
Surgery in	
(a) Diabetes	Sugar, CO_2
(b) Nephritis	Urea, creatinine, CO_2
Pyloric obstruction	CO_2, Cl, urea
Intestinal obstruction	CO_2, Cl, urea
(a) High	CO_2, Cl, urea
(b) Low	Urea, creatinine, CO_2, Cl
Peritonitis	Urea, CO_2
Toxemias of pregnancy	Urea, CO_2, urie acid
Toxemias of malignancy	Urea, CO_2
Pancreatic disease	Sugar, diastatic activity, icteric index
Cholecystitis	Sugar, diastatic activity, icteric index
Liver conditions	Icteric index, sugar, urea
Tetany after thyroidectomy	Ca
Fractures	P, Ca
Urological conditions	
(a) Prostatic obstruction	Urea (creatinine), CO_2
(b) Bladder tumors	Urea (creatinine), CO_2
(c) Renal calculi	Urea (creatinine), CO_2
(d) Nephrectomy	Urea (creatinine), CO_2
(e) Double polycystic kidney	Urea (creatinine), CO_2

Various pathologic conditions in which a chemical blood analysis may give helpful information are listed in Table II, together with the determinations which appear to be most indicated. Only the more simple determinations have been included. Every reasonably well equipped hospital laboratory should be prepared to make these determinations. Chemical blood analysis is not difficult, but it does require more than an ordinary amount of chemical skill in addition to a fundamental knowledge of chemistry. I have been disgusted more than once at the unsatisfactory way in which such determinations are handled in many institutions, thus rendering the determinations useless, or worse than useless. Quite aside from the analytical part, the laboratory should be furnished with an adequate amount of blood, 15 to 20 c.c., in which clotting has been prevented with a fairly definite amount of potassium oxalate, and given a tentative diagnosis so that the best possible use can be made of the material.

Acidosis and Alkalosis.—The subject of acidosis and alkalosis is so important from a surgical point of view that it demands specific emphasis even at the point of repetition. The clinical symptoms of acidosis and alkalosis are almost identical. I recall a fatal case in which alkalosis was preesnt (as shown by the CO_2 and P_H), though not recognized by the surgeon. Three separate consultants prescribed gastric lavage and $HNaCO_3$. With a CO_2 capacity above 45 vol. per cent the prognosis is good. Severe acidosis (CO_2 below 33 vol. per cent in which case the condition is uncompensated, i.e., the P_H falls below 7.35 and may go to 7.0) may be found in diabetes, nephritis, eclampsia, carcinoma, and various urologic conditions. Operative interference

in such cases under a general anesthetic would most likely lead to death. In conditions other than diabetes where insulin is a specific, some temporary benefit may be obtained from sodium bicarbonate administration often with added glucose. For a unit of weight of 42 pounds, 0.5 gm. of $HNaCO_3$ generally raises the CO_2 capacity 1 vol. per cent. Overdosing with $HNaCO_3$ will lead to alkalosis, and the surgeon should guard against this as the condition is more difficult to treat than acidosis, although $CaCl_2$ and NH_4Cl may be given orally to combat the alkalosis. With pyloric or high up intestinal obstruction, a very severe alkalosis may develop, due apparently to the loss of HCl in vomiting. Here the blood changes and clinical symptoms may be more severe than in overdosing with sodium bicarbonate.

Surgery in Diabetes and Nephritis.—The surgeon is not infrequently called upon to operate upon patients suffering from diabetes or nephritis, adding to the risk of the operation. A preoperative blood chemistry should always be secured in such individuals. Although the use of a general anesthetic upon a diabetic is not attended with the dangers which existed before the advent of insulin, still definite information should be available as to the level of the blood sugar and, if this has been running at a high level (above 0.25 per cent), a CO_2 capacity determination should be made. If possible, both the sugar and CO_2 should be brought within normal limits before operation. Diabetics with infections frequently do not respond well to insulin and this should be borne in mind.

In operating upon patients suffering from renal disease the surgeon needs definite information on nitrogen retention and any possible acidosis. This is best furnished by the blood urea nitrogen and CO_2 capacity. A urea nitrogen below 20 mg. per 100 c.c. and a CO_2 capacity above 45 volumes per cent may be regarded as giving a favorable operative prognosis. With an increase in the nitrogen retention and acidosis, the outlook becomes less and less favorable. Where there is considerable nitrogen retention and a CO_2 as low as 30 volumes per cent, the patient may not survive the operation.

Pyloric Obstruction.—With pyloric obstruction, such as often occurs in peptic ulcer and other conditions, the acid-base equilibrium may be badly disturbed, owing in part to the loss of HCl by vomiting. Typical and severe symptoms of alkalosis may develop (headache, nausea and vomiting, dizziness, vertigo, and light-headedness), which will be relieved only upon removal of the obstruction by gastroenterostomy or otherwise. Such patients will show a high CO_2 capacity (above 70 volumes per cent) and a low plasma chloride (below 550 mg.). The P_H may exceed 7.6. They may or may not show nitrogen retention. Temporary relief may be afforded by the intravenous administration of NaCl.

Intestinal Obstruction, Peritonitis, Duodenal Ulcer.—With *high up intestinal obstruction* and vomiting the symptoms may be very similar to those found in pyloric obstruction. The chemical blood determinations indicated would be the same. With *obstruction lower down* in the intestine the disturbance of the acid-base equilibrium is not as great, but the nitrogen retention may be very marked, equal to that observed in many cases of severe nephritis. Rabinowitch[5] considers the outlook grave when the urea nitrogen

exceeds 50 mg. Along with the nitrogen retention there is a depletion in chloride. As pointed out by Haden and Orr,[3, 4] the intravenous administration of NaCl may temporarily relieve the patient so as to permit a successful operation, which would otherwise have been impossible. In *peritonitis* the nitrogen retention may be quite as marked as in intestinal obstruction. Many cases of *duodenal ulcer* show moderately elevated figures for blood urea nitrogen (20-25 mg.).

Toxemias of Pregnancy.—In contradistinction to true nephritis, the urea nitrogen in eclampsia is normal or decreased, although the nonprotein nitrogen may be moderately elevated. Along with the reduction in the blood urea there is generally a considerable elevation in the blood uric acid, both changes probably depending upon the liver. Urea nitrogen figures of 5 to 10 mg. in comparison with the normal of 12 to 15 mg. may be observed, while the uric acid may be elevated from an upper normal between 3 and 4 mg. to 5 to 12 mg. In severe cases of eclampsia the CO_2 may be markedly reduced. Toxemias do occur in which nitrogen retention exists but it seems probable that in most cases this is due to a true nephritis, an important point in preoperative differential diagnosis.

It is well to bear in mind that in normal pregnancy the nonprotein and urea nitrogen yield low normal values, and that the moderately reduced carbon dioxide in the blood is the result of an uncompensated alkalosis, due to increased ventilation, and not to a true acidosis.

Toxemias of Malignancy.—Although many systemic disturbances may be detected in the terminal stages of malignancy, probably the most important are nitrogen retention and acidosis.

Pancreatic Disease, Cholecystitis.—Pancreatic disease is almost invariably accompanied by some increase in the blood sugar and a considerable elevation in the diastatic activity. These findings together with the symptomatology may help to establish the diagnosis. An estimation of the icteric index should also be made. In many cases of cholecystitis there is pancreatic involvement resulting in hyperglycemia and some increase in the diastatic activity.

Liver Conditions.—The icteric index is probably the most useful single test of liver function.[6, 7] It helps in the diagnosis of cases of cholecystitis and cholelithiasis without clinical jaundice; aids in distinguishing between obstructive jaundice due to malignancy and catarrhal jaundice by showing whether the jaundice is increasing, diminishing or stationary; is helpful in the diagnosis of cirrhosis and malignant metastases in the liver, and determines whether obstructive jaundice has been relieved by operation. The van den Bergh qualitative test distinguishes between obstructive and nonobstructive jaundice and helps to detect any false positive results with the icteric index, since it is specific for bilirubin. In obstructive jaundice, cholesterol is increased, while in cholecystitis the bile acids are raised to about five times the normal. In some cases of cirrhosis of the liver the blood sugar is reduced to a very low figure, 50 mg. or less.

Tetany after Thyroidectomy.—The tetany which sometimes occurs after partial resection of the thyroid and consequent loss of parathyroid tissue is

due to a reduction of the serum calcium below the critical level of about 7.5 mg. A serum calcium estimation must be made to definitely establish the diagnosis, and should be repeated during the subsequent treatment until the calcium returns to normal.

Fractures.—According to the observations of Tisdall and Harris[8] a fracture normally provokes a rise in the level of inorganic phosphorus and calcium of the blood serum to the level found during infancy, i.e., of P from 3 to 4-6 mg. and Ca from 10 to 10.5 mg. Cases of nonunion are probably due to a lack of mobilization of inorganic P and Ca. Ultraviolet light or viosterol is indicated in such conditions.

Urologic Conditions.—Preoperative information on the chemistry of the blood has been found of great value in all surgical conditions of the kidneys, bladder, or prostate,[9, 10] but it seems to be of special value in *prostatic obstruction.* Of the different chemical blood tests, the urea is the most helpful, although with urea retention, the creatinine, or CO_2 capacity may be more significant. When the urea nitrogen is 20 mg. or under, the renal factor can be disregarded. Uncomplicated cases show urea nitrogen figures which on the average are definitely above the normal of 12 to 15 mg. per 100 c.c. of blood. The average is probably about 18 mg., with a range of 11 to 25 mg. Patients presenting urea nitrogen figures over 25 mg. should be operated upon with caution and best after a period of preliminary treatment directed to relieve the nitrogen retention. These patients are not the best operative risks, but many such patients can be operated upon with satisfactory results after a more or less prolonged period of preoperative treatment which favorably influences the blood urea. Patients with a marked nitrogen retention, who do not readily yield to treatment, are suffering from advanced renal disease and are obviously poor surgical risks. Operative interference almost invariably provokes a rise in the blood urea in uncomplicated cases of prostatic obstruction. It is easy to comprehend the effect on a badly damaged kidney.

The blood findings in *vesical neoplasms*, whether malignant or nonmalignant, are similar to those found in prostatic obstruction, the urea nitrogen on the average being only slightly increased, if we except those cases which show definite evidence of nitrogen retention. The experience of Squire, Bandler and Myers[9] indicates that urea nitrogen figures of over 30 mg. afford an unfavorable prognosis in carcinoma of the bladder, irrespective of the therapeutic procedure.

While blood analyses indicate the conditions of both kidneys, they are of value in determining the operability of patients with unilateral renal lesions. In such cases, the blood findings are usually within normal limits. However, in lesions necessitating *nephrectomy*, the toxemia produced by the renal infection sometimes temporarily impairs the function of the other kidney, so that the urea nitrogen may be 30 mg. or more. When the diseased kidney has been removed, however, the urea drops to normal.

In bilateral *nephrolithiasis* in which nephrotomy and nephrectomy are indicated, the information obtained from the blood, coupled with the separate phenolsulphonephthalein excretion, is of great prognostic value.

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BLOOD CHEMISTRY AND THE GASTROINTESTINAL TRACT*

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MUCH of the progress that has been made in medicine during recent years has been due to the development and clinical application of microchemical methods for the examination of the blood. Through chemical studies of the blood our viewpoint concerning the nature of some of the most serious disturbances of the gastrointestinal tract has been entirely changed and the treatment of such disorders has been revolutionized, with great advantage to the patient. The clinical conditions in the case of which blood chemistry studies are most important are those conditions which are associated with disturbances in motility accompanied usually by an abnormal loss of the gastrointestinal secretions, such as: (1) obstruction of the (a) small intestine, (b) pylorus, and (c) esophagus; (2) vomiting without obstruction; (3) fistula of the upper intestinal tract; (4) prolonged diarrhea from any cause; (5) paralytic ileus; and (6) acute peritonitis.

In all of these various clinical conditions a rather characteristic toxemia is present and in all of them, also, the chemical changes which take place in the blood and urine are of a somewhat similar nature. Intestinal obstruction is a condition which is found frequently and has been intensively studied for many years. Long before it was known that characteristic chemical changes take place in the blood, the toxemia of intestinal obstruction was considered to be due to the absorption of putrifying organic material from the lumen of the obstructed gut. Hartwell and Houget in 1910[1] concluded that dehydration was the most important factor in the toxemia of intestinal obstruction because the life of a dog in the case of which the small intestine had been obstructed experimentally could be prolonged by the administration of fluid in the form of a physiologic saline solution. In 1914 Tileston and Comfort[2] observed a marked increase in the nonprotein nitrogen of the blood in patients suffering from intestinal obstruction. This observation was verified by Whipple and his coworkers[3] in an experimental study of intestinal obstruction. Whipple[4] also found an increased destruction of protein as evidenced by the increase in excretion of nonprotein nitrogen, and concluded that the existing toxemia was due to the absorption of a toxic protein derivative from the wall of the obstructed gut. The other constituents of the blood showed no significant variation from normal.

Further clinical and experimental studies by Haden and Orr[5] showed, in addition to changes in the nitrogenous bodies, very striking variations in the blood chloride and bicarbonate. After experimental obstruction had been brought about in which the changes could be followed from the onset, there was found to be a progressive fall in the blood chlorides. As the chlorides

*From Cleveland Clinic.

are lost there is usually a rise in the carbon dioxide capacity of the plasma since the sodium which is left behind as a result of the loss of chloride combines with the carbon dioxide which is constantly present, thus increasing the circulating sodium bicarbonate. The level of the bicarbonate is very variable since it is dependent upon several factors other than the release of the sodium from its combination with the chloride. The fall in chloride is certainly partly due, and probably largely due to the mechanical loss through vomiting. At the same time dehydration increases. As this process continues an increase in protein destruction is shown by an increase in the nonprotein nitrogen of the blood and the urine.[6] The mechanical loss of fluids and salts with consequent dehydration may be largely responsible for the clinical picture and laboratory findings in cases of intestinal obstruction, yet it is also possible that the toxemia may be due, in part at least, to the absorption of some toxic body or bodies which destroy tissue protein. The increase in nonprotein nitrogen is certainly not due entirely to a retention from kidney insufficiency. The sugar and other constituents of the blood show little variation from the normal. The marked decrease[6] in the oxygen saturation of the venous blood is due largely to the slowed circulation rate, although it is conceivable that some reducing body may be a factor also.

The characteristic changes in the blood in the presence of intestinal obstruction, then, are (1) dehydration, (2) hypochloremia, (3) alkalosis, (4) increased nonprotein nitrogen, (5) accelerated tissue catabolism with increased nitrogen excretion, and (6) decreased oxygen saturation of the venous blood. In simple intestinal obstruction which has been brought about experimentally, a toxemia may be prevented by supplying sufficient fluid daily from the onset of the obstruction, in the form of physiologic salt solution; when the toxemia is well advanced the condition may be relieved by giving a hypertonic solution.[7] In clinical work often the dehydration has become very marked and the chloride store of the body greatly depleted, before the patient is first seen; in such cases it is wise to give a 3 per cent solution of sodium chloride which should be administered in 10 per cent glucose since food is always necessary. An operation should never be attempted in the case of a patient in whom an intestinal obstruction is present until a sufficient amount of fluid and salt has been given to overcome the dehydration and hypochloremia.

In the presence of pyloric obstruction[8] the chemical changes are the same as those which are characteristic of intestinal obstruction. Pyloric obstruction develops more slowly than intestinal obstruction and is often allowed to progress for a longer time before operative interference is instituted. The alkalosis and hypochloremia are usually more marked since there is a greater loss of chloride by vomiting. The dehydration, the increase in nonprotein nitrogen, and the decrease in oxygen saturation of the blood, are striking. This condition should be treated in the same way as intestinal obstruction.

Experimental obstruction of the cardia and lower end of the esophagus[9] causes dehydration, an extremely rapid rise in the nonprotein nitrogen of the blood, and a decrease in oxygen saturation, but not much change in the chloride or carbon dioxide combining power of the plasma. The toxemia

which may accompany this condition can also be entirely prevented by the proper use of a salt[10] solution. A case of this type is seldom seen clinically.

A fistula[11, 12] in the upper intestinal tract will bring about the blood changes which are characteristic of intestinal and pyloric obstruction. In this case there is an excessive loss of fluid and chloride, the nonprotein nitrogen rises rapidly and dehydration is very marked. The extent of these changes can be gauged only by a chemical study of the blood and the treatment must be based on the findings.

Prolonged vomiting from any cause such as the toxemia of pregnancy[13] will produce the same chain of events. In every case of vomiting the blood should be carefully studied and the treatment which is indicated by the findings should be given. In the case of paralytic ileus definite changes are often found in the blood although not to so marked a degree. Here the use of a hypertonic solution is of value not only for its general effect but especially for its marked effect in stimulating peristalsis.[14]

In the presence of peritonitis[15] the chloride content becomes less. In this case also the nonprotein is increased and dehydration develops. For this condition the proper use of salt solution is of the greatest value just as it is in an uncomplicated case of paralytic ileus.

The chemical changes in the body which are the result of diarrhea and vomiting have been studied by Hartmann.[16] In the case of diarrhea much fluid may be lost, causing a dehydration which may be serious enough to result in renal insufficiency. If there is no vomiting, the blood chemistry problem, as far as the acid-base balance is concerned, is quite different from that which is found in a case of intestinal obstruction. The bicarbonate is decreased and the chloride is increased, therefore, the administration of sodium bicarbonate solution instead of sodium chloride solution, is indicated.

If both vomiting and diarrhea occur a decrease in bicarbonate is evidenced by the fall in carbon dioxide combining power, and a decrease in the chlorides if the gastric secretions contain free hydrochloric acid. In such conditions, however, often very little hydrochloric acid is secreted so that

TABLE I

CLINICAL CONDITION	BLOOD CHEMICAL FINDINGS				TREATMENT INDICATED
	DEHYDRATION	NONPROTEIN NITROGEN	SODIUM CHLORIDE	CARBON DIOXIDE COMBINING POWER	
Intestinal obstruction	+++	+++	−−−	+++	Hypertonic (1 to 3%) sodium chloride in 10% glucose solution
Pyloric obstruction	++++	++++	−−−−	++++	Same
High intestinal fistula	+++	+++	−−−	+++	Same
Paralytic ileus	+	+	−	0	Hypertonic (3%) sodium chloride solution
Peritonitis	++	++	−	−	Hypertonic (1 to 3%) sodium chloride in 10% glucose solution
Diarrhea only	+++	+++	+	−−−	Sodium bicarbonate (5%) intravenously
Diarrhea and vomiting	+++	+++	0	−−−	Same
Cardiac obstruction	++++	++++	−	−	Sodium chloride (1%)

the fall in bicarbonate is much more marked than is the fall in chloride.[16] Here again the indications for treatment are demonstrated only by a careful study of the blood chemistry.

In Table I the characteristic changes which take place in the presence of the conditions which have been discussed, are summarized, and the preferred treatment is indicated in each case.

SUMMARY

In all cases of disturbances in motility of the gastrointestinal tract of the types described in this paper, the ideal procedure is to determine:

1. The extent of dehydration, which is done by the use of the hematocrit, and by the estimation of the amount of plasma protein.

2. The amount of circulating bicarbonate, which is done by estimating the carbon dioxide combining power of the plasma.

3. The amount of plasma or whole blood chloride.

4. The level of nonprotein nitrogen in the whole blood.

In cases of intestinal and pyloric obstruction the chlorides are usually lost out of all proportion to other elements, indicating the administration of a hypertonic solution of sodium chloride, given with glucose preferably. Similar treatment is indicated in excessive vomiting in the absence of obstruction or of diarrhea, and also in cases of paralytic ileus.

Cases of cardiac obstruction in which concentration is evident, without loss of salts, are best treated by the administration of 1 per cent sodium chloride given intravenously.

If dehydration is due to diarrhea only or to diarrhea accompanied by vomiting with little hypochloric acid in the gastric secretions, the blood shows an increase in chloride but a great decrease in sodium bicarbonate. The condition must be treated by the intravenous administration of sodium bicarbonate with or without glucose.

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FUNCTIONAL TESTS IN THE SURGICAL DIAGNOSIS AND TREATMENT OF DISEASES OF THE LIVER AND BILE DUCTS*

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TESTS of function are of value to the surgeon, primarily in proportion to the extent to which they serve: (1) to establish or confirm a diagnosis already made on clinical grounds; (2) to warn of operative or postoperative complications which may be met or avoided by appropriate preoperative measures; and (3) to indicate the risk of operation. It is the exception rather than the rule for any one test to be so inclusive and of such far-reaching significance that the results cover these different categories. This is particularly true when an organ with the manifold activities of the liver is considered.

Physiologic study of the liver has indicated that the activities of this organ may be divided into: (1) those concerned in the intermediary metabolism of the body, with especial reference to the metabolism of carbohydrates, of proteins and of fats; (2) those concerned with the formation and excretion of bile, with particular reference to bilirubin, the bile acids, cholesterol, and elimination of various dyestuffs which are excreted in the bile, and (3) those which are much less well understood, but which have been ascribed to the liver, or in which the part the liver plays, although important, is not necessarily predominant. The detoxification of many substances in the body, and regulation of the coagulation of the blood, are examples of this latter group of activities.

We have summarized previously many of the proposed tests of hepatic function, and have described the laboratory technic of these different tests.[8] Mann and Bollman have also reviewed this subject with particular reference to tests involving the intermediary metabolism of carbohydrates and proteins. The majority of hepatic functional tests fail, however, to conform to the criteria of usefulness just outlined, and a detailed review of the literature at the present time is unnecessary. The few tests of hepatic function which are of definite clinical value are best considered in relation to the various types of disease involving the liver and biliary tract.

Disease of the gall bladder is frequently associated with chronic inflammatory processes in the liver or biliary passages. In the ordinary case of cholecystitis the effects of these associated changes on the functional efficiency of the liver are minimal and may be disregarded.[9] The introduction of cholecystography by Graham and Cole in 1924 constituted a marked advance in the roentgenologic diagnosis of disease of the gall bladder. Kirklin[16, 17] has recently described the various technical details essential to the

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successful use of this method and has given a general appraisal of its status at the present time. The microscopic study of the bile obtained by duodenal drainage is also important. Bockus and his associates found the presence of crystals of cholesterol or deposits of calcium bilirubinate to be indicative of cholecystic disease. Both tests are of value as aids to the clinician, but it must be recognized that the final diagnosis, and the decision as to the necessity for operation, devolve on the clinician and surgeon and not on the laboratory.

Apart from cholecystitis, the diseases involving the liver and biliary tract may be divided symptomatically into those diseases associated with jaundice or potential jaundice, and those associated with ascites or potential ascites. Rich recently reviewed the pathogenesis of jaundice and considered the various types in detail. From the clinical standpoint, however, jaundice may be considered as consisting of three main types: (1) hematogenous; (2) hepatogenous and (3) obstructive. The last may be due to blocking of the extrahepatic biliary passages by stones, by inflammatory strictures, or by a tumor either of the duct itself or of adjacent structures such as the head of the pancreas. In clinical practice one sees many intermediate or mixed types of jaundice, but one or another of the processes mentioned predominates. Tests of hepatic function have a definite place in the clinical study of these various types of jaundice.

McVicar and Fitts reported that the essentials for diagnosis, if a patient is jaundiced, include a consideration of the presence or absence of pain, and its character when present, information as to the patency of the biliary passages as shown by study of the stools and the duodenal content, the van den Bergh reaction in the blood serum and the level and variability of the curve of serum pigment. With the data mentioned a working diagnosis usually can be established, and surgical and nonsurgical varieties of jaundice can be distinguished from each other.

Hemolytic icterus, either congenital or acquired, constitutes the main example of a predominately hematogenous type of icterus that is of surgical importance. It is also the only variety of jaundice in which laboratory studies furnish pathognomonic information. W. J. Mayo was one of the first to recognize the importance of splenectomy in the treatment of this condition. During the last six years splenectomy for hemolytic jaundice has been performed at The Mayo Clinic on sixty-three patients without a death.

The experimental studies of Mann, Sheard, Bollman and Baldes have demonstrated the part played by the spleen in destruction of erythrocytes and in formation of bilirubin. Van den Bergh and Snapper, Kaznelson, Rich and Rienhoff and numerous other observers have investigated the bilirubin content of the blood from the splenic artery and vein. Ordinarily the amount of bilirubin in the blood from the splenic vein is the same as or but slightly increased over that in the blood from the splenic artery, but in hemolytic jaundice the increase may be 3 or 4 mg. in each 100 c.c. We[11] have obtained similar results. These studies furnish an adequate physiologic explanation of the benefits derived from splenectomy in such cases.

In uncomplicated cases of hemolytic jaundice the pertinent laboratory data are the anemia and microcytosis, the high reticulocyte count, and the increased fragility of the erythrocytes. The concentration of serum bilirubin, and the icterus index, are increased to a moderate degree, the former rarely exceeding 10 mg. in each 100 c.c. The van den Bergh reaction is persistently indirect. This association of clinical jaundice with an indirect van den Bergh reaction is diagnostic of a hemotogenous type of jaundice. The coagulation of the blood is not disturbed. There is no retention of bromsulphalein or phenoltetrachlorphthalein. Duodenal drainage usually discloses a free flow of bile, with an increased content of bilirubin. The urine contains large amounts of urobilin and urobilinogen, but bilirubin is absent.

The increase in the excretion of bile pigments associated with hemolytic jaundice often leads to the deposition of small pigment calculi in the biliary tract. Gallstones were found in 58 per cent of the series of cases of hemolytic jaundice reported by Giffiin in 1917. When these calculi lodge in the common or hepatic ducts, then the symptoms and laboratory data characteristic of obstructive jaundice are superimposed on other manifestations and a confused clinical picture may result. In a case in which operation was proposed in 1925, splenectomy was performed and a stone 1.5 cm. in diameter was removed from the ampulla of Vater, at the same time. The patient recovered uneventfully and has remained well. In such a case the laboratory tests may be misleading and the laboratory criteria for hemolytic jaundice can be relied on only when the biliary passages are patent.

Obstructive jaundice presents a different picture from both the laboratory and the clinical standpoints. The three common clinical varieties, those due to calculus, cicatrix, and carcinoma, are all associated with an elevated concentration of serum bilirubin and a direct van den Bergh reaction. There is usually moderate anemia of the secondary type, and decreased fragility of the erythrocytes. A hemorrhagic tendency is frequently present in all types of obstructive jaundice, as shown most commonly by prolonged coagulation time and occasionally by thrombocytopenia. The bromsulphalein and tion roughly parallels the degree of serum jaundice. In many cases the other dye tests are almost invariably strongly positive; the degree of retenretention of dye persists after the serum bilirubin has returned to a normal level although the van den Bergh reaction is still direct. The duodenal tube usually produces a fairly free flow of bile in cases of choledocholithiasis and if drainage is done repeatedly, complete obstruction will be demonstrated infrequently in this variety of obstructive jaundice. In obstruction due to stricture, the biliary flow is usually scanty, whereas in cases with malignant lesions of the ducts, bile usually is absent in the material obtained by duodenal drainage. There is rarely any necessity for quantitative studies of the amount of bilirubin in the material obtained by duodenal drainage; the changes mentioned are sufficiently striking to be apparent on casual examination. Examination of the stool usually gives information to confirm the results of duodenal drainage mentioned. Bile pigment is present in the urine in all types of obstructive jaundice, and bile salts can usually be demonstrated by the Hays or Pettenkofer test. Tests for urobilin and urobilino-

TABLE I

FUNCTIONAL TESTS IN DIFFERENT DISEASES OF LIVER AND BILE DUCTS

	BLOOD								BROMSULPHALEIN TEST, RETENTION OF DYE, GRADE	DUODENAL DRAINAGE, BILIARY PIGMENTS	URINE	
	HEMOGLOBIN, CONCENTRATION	ERYTHROCYTES NUMBER	RETICULOCYTES, PERCENTAGE	FRAGILITY OF ERYTHROCYTES	COAGULATION TIME	VAN DEN BERGH TEST	SERUM BILIRUBIN CONCENTRATION	ICTERUS INDEX			BILIRUBIN	UROBILIN
Hemolytic icterus	Decreased	Decreased	Increased	Increased	Normal	Indirect	Increased	High	None	Much increased	None	Present
Obstructive jaundice												
Stone	Decreased	Decreased	Normal	Decreased	Increased	Direct	Increased	High	Marked	Decreased	Present	Present
Stricture	Decreased	Decreased	Normal	Decreased	Increased	Direct	Increased	High	Marked	Decreased	Present	Present
Carcinoma	Decreased	Decreased	Normal	Decreased	Increased	Direct	Increased	High	Marked	Complete obstruction	Present	None
Hepatitis	Decreased	Decreased	Normal	Decreased	Increased	Direct	Increased	High	Marked	Variable	Present	Variable
Cirrhosis	Decreased	Decreased	Normal	Normal	Normal	Variable	Variable	Variable	Variable	Normal or decreased	Variable	Present

gen give variable results and seem to depend on the amount of bile pigment which enters the intestine.[1, 25]

We have found isolated or single determinations of serum pigment in cases of obstructive jaundice to be much less significant than the determination of the curve of serum pigment, and its variation from day to day, which give results of much greater clinical significance. In cases of obstruction due to stone, the bilirubin content of the serum is usually only moderately elevated, but it may show considerable variation from day to day. Colic usually is followed by a sharp increase in serum pigment, whereas, if the obstruction is released, an equally sudden decline may occur. In obstruction due to stricture there is usually a good deal of associated biliary cirrhosis, and low fixed curves of serum pigment are the rule. Occasionally there may be periods of intermittent obstruction, with a corresponding elevation of the value for serum bilirubin. Since carcinoma usually produces complete obstruction, high and rising curves of serum bilirubin are most commonly found in the presence of carcinoma. These curves of serum pigment are of considerable significance to the surgeon in selecting a favorable time for operation. The surgical risk appears to be at its lowest, with a stationary or a rapidly falling curve of bilirubin, whereas it is apparently greatest with suddenly developing jaundice and a high or rising value for serum bilirubin. As has been shown in the experimental animal, the curve of serum bilirubin eventually tends to strike a level or to decline if obstruction is complete or nearly so and a surgeon may often elect to wait until this stabilizing process is complete before intervening in any given case of biliary obstruction. In a proved case of obstructive jaundice, surgical intervention is indicated whenever the condition of the patient permits and the risk is not prohibitive.

Hydrohepatosis, and infection of the biliary parietal sacculi, which McIndoe and Counseller have demonstrated in this condition, are capable of producing much injury to the hepatic parenchyma and can be corrected only by surgical measures. We have also reported on the composition of the bile following the relief of biliary obstruction.[13, 29] These studies give further evidence of the functional injury to the liver in consequence of biliary obstruction. When the liver is not too greatly injured the character and composition of the bile rapidly return to normal. After long-continued obstruction, or in the presence of considerable infection, this return is greatly delayed.

The degree of hepatic injury produced by biliary obstruction cannot be measured by any functional test known to us. Dye tests are obscured by the presence of jaundice and biliary obstruction, and cannot be relied on. The concentration of bile salts in the serum has been studied and does not give additional information of value. The same may be said of studies of blood cholesterol, although further work on this subject is necessary before it can be completely dismissed from consideration.

The two barriers to successful surgical treatment are hepatic insufficiency and hemorrhage, and the liability to either is most difficult to estimate. The danger of postoperative hemorrhage in the jaundiced patient has long been recognized. The determination of the coagulation time of the blood is of im-

portance, for delayed coagulation indicates the need for care to prevent this complication. Petechial or purpuric hemorrhages afford further danger signals. A prolonged coagulation time is not an absolute contraindication of surgical measures, and postoperative bleeding may occur if a patient has a normal coagulation time. In the absence of more satisfactory information regarding the particular factors responsible for this phenomenon the determination of the coagulation time of the blood is the most satisfactory laboratory test available at the present time.

Walters has shown the importance of adequate preoperative preparation in preventing postoperative hemorrhage in cases of jaundice. He reported the beneficial results secured by intravenous injection of calcium chloride solution, and these conclusions have been amply confirmed by surgical experience. The interference in blood clotting has been thought to be due to some abnormality of the serum calcium, but this is probably not correct, for Snell and Greene, and Gunther and Greenberg have not been able to demonstrate significant changes in either the total or diffusible calcium present in the serum in jaundice. Injections of calcium chloride will not control the tendency to hemorrhage in all cases of jaundice. In such cases transfusions of blood must be relied on to accomplish the desired result, and should be repeated if necessary.

Renal insufficiency is an occasional accompaniment of jaundice and, as Walters and Parham pointed out, it usually develops as a terminal or postoperative condition. The determination of the concentration of blood urea is of value in following the progress of the renal condition and to warn of the development of uremia. The value of intravenous administration of a solution of glucose, 10 per cent, and sodium chloride, 1 per cent, in combating this condition is well known and needs no further comment. The studies of Walters, Greene and Fredrickson[13, 29] also show the importance of an adequate supply of sodium chloride and of fluids in the treatment of the postoperative hepatic insufficiency associated with cholerrhagia.

In jaundice due to lesions of the hepatic parenchyma, the so-called hepatogenous, or intrahepatic type, the laboratory data do not differ greatly from those described in obstructive jaundice. It is unusual in this group of cases for bile to be completely absent from the intestine for any great length of time, so that duodenal drainage usually gives a positive result except in the earlier stages of the acute varieties. Cases of intrahepatic jaundice fall roughly into three groups and these present more or less characteristic curves of serum bilirubin. In acute varieties, the most common of which are designated as "epidemic" or "catarrhal" jaundice, usually there is a rapid rise of the value for serum bilirubin at the onset, and a gradual fall, the whole process extending over a period of from two to six weeks. In acute or subacute yellow atrophy, high fixed curves of serum bilirubin are common. In this group very high levels of serum bilirubin may be encountered, in fact, any value of 25 mg. for each 100 c.c. or more should lead to the suspicion of extensive hepatic degeneration. In the more chronic forms of hepatic disease, corresponding to the various forms of cirrhosis, values for serum bilirubin from 5 to 10 mg. in each 100 c.c. are the rule, and the value changes only slightly from day to day. Since most cases of intrahepatic jaundice tend

either to progress or to clear up spontaneously within a month or six weeks, it is good practice to observe suspected cases over this period before deciding on surgical intervention. In other words, only the more chronic forms of intrahepatic jaundice need to be considered from the standpoint of operation. This group of cases presents great diagnostic and therapeutic difficulties, and exploration may be required to settle the question of the possible presence of a stone in the common bile duct. The same dangers, hepatic insufficiency and hemorrhage, confront the surgeon in these cases as in cases of obstructive jaundice, and preoperative study and preparation must be carried out with the same care.

The differential diagnosis of intrahepatic and obstructive jaundice must be made primarily on the basis of an accurate history and a careful general examination. Laboratory tests alone cannot always be relied on. Stones may be entirely silent (5 per cent of all cases), and colic-like pains may occur in cases of hepatitis or of carcinomatous obstruction to the common bile duct. Age is not an entirely reliable criterion, for we have seen a man aged seventy-one years, who had what was clinically a typical acute hepatitis or catarrhal jaundice. Carcinoma may occur in young adults but is very rare in persons who are less than thirty-five years. The course of the jaundice, likewise, is not an entirely reliable guide, since it depends on the degree of biliary obstruction. Although intermittent jaundice is usually indicative of stones, we have seen it in association with carcinoma, both of the hepatic ducts and of the head of the pancreas, and with cirrhosis. Hepatitis may be associated with acholic stools and the absence of urobilin and urobilinogen in the urine for several days. Because of these difficulties a satisfactory clinical diagnosis may be impossible. In such cases surgical exploration of the biliary passages is advisable if the condition of the patient permits.

Various laboratory tests have been proposed at one time or another as reliable guides to the differentiation of obstructive and intrahepatic jaundice. Changes in carbohydrate metabolism in association with hepatic disease have been sought assiduously since the discovery by Claude Bernard of the glycogenic function of the liver. These changes are easily shown in experimental animals. Changes in the tolerance to carbohydrate as measured either by the degree of glycosuria or the elevation of the blood sugar after the giving of glucose, fructose or galactose are readily demonstrable in dogs after ligation of the common bile duct or the administration of various hepatic poisons, such as chloroform or phosphorus. Diminution in the glycogen content of the liver is readily shown in these same conditions. Mann and Bollman have stressed the significance of hypoglycemia occurring in dogs following surgical removal of the liver.

These observations have their clinical counterparts. We do not question but that there may be considerable disturbance of carbohydrate metabolism in cases of hepatic disease. This is amply confirmed by clinical observations which show the importance of a diet rich in starches and other carbohydrates in the preoperative preparation of jaundiced patients and by the usefulness of the intravenous injection of solutions of glucose in the treatment of postoperative collapse in these same conditions. Actual hypo-

glycemia arising from depletion of the glycogen stores in the liver is, however, a rare clinical entity. It has occurred as a recognizable clinical entity in only three cases in our experience. Although we admit that disturbances in carbohydrate metabolism may be present if patients have jaundice, the disturbances either are not sufficiently great, or the available laboratory tests are neither sufficiently sensitive nor specific to be of diagnostic value. Much has been written regarding the value of such tests, particularly of the galactose tolerance test, in distinguishing jaundice due to biliary obstruction from jaundice due to hepatitis or toxic injury to the parenchymal cells of the liver. Our own experience has not confirmed these views and we have found the various tests of sugar tolerance to be of questionable value for such distinction.

Jaundice is the outstanding clinical symptom in one group of hepatic diseases, and in these the determination of the serum bilirubin, its reaction to the van den Bergh test, and its fluctuations throughout the course of the disease, are of great practical diagnostic value. In diseases of the liver not associated with jaundice the bromsulphalein test gives reliable information on a number of points referable to both diagnosis and therapeutic indications.

In portal cirrhosis, the bromsulphalein test may be particularly helpful.[11] In the occasional case of the disease which may be recognized in its preascitic stage, it is usually the dye test which gives the earliest and most accurate diagnostic clue. When the disease has reached the stage of ascites, dye tests are almost invariably positive (80 of 87 cases reported by Chapman, Snell and Rowntree). The degree of retention of dye is remarkably constant in any given case, provided jaundice is not present. In exceptional instances there is a reduction in the degree of retention of dye as the patient improves. The results of bromsulphalein tests in portal cirrhosis are so constant that one should be cautious in attributing ascites to a hepatic lesion in the absence of such a positive test. With a negative test other conditions should be carefully sought. The prognosis in portal cirrhosis may also be determined, to some extent at least, by the bromsulphalein tests. In the series reported by Chapman, Snell and Rowntree the average duration of life appeared to vary inversely with the degree of retention of bromsulphalein. This fact is of much value to the surgeon in the determination of the surgical risk when Talma-Morison omentopexy, splenectomy, or ligation of the coronary veins of the stomach is under consideration. Greene and Conner have also emphasized the importance of this test as a guide to surgical risk in cases of splenic anemia or Banti's disease.

Other pathologic changes in portal cirrhosis include secondary anemia of moderate severity, and, in the so-called Banti's group, marked leucopenia. This anemia may, of course, be modified by the presence or absence of bleeding from esophageal varices. There is no characteristic disturbance in the fragility or the coagulation time of the blood. The value for serum bilirubin and the icterus index may be slightly increased. If so, the van den Bergh reaction usually is direct, but in many cases the concentration of serum bilirubin is decreased and an indirect van den Bergh reaction is present.

The urine frequently is of dark color and contains urobilin and urobilinogen, but bilirubin is uncommon.

In one other field the bromsulphalein test serves the surgeon particularly well. When a neoplasm has been demonstrated in the gastrointestinal tract, and a search for metastasis is under way, the liver should not be overlooked. We have previously pointed out that[10] a dye test is often positive in the early stages of hepatic involvement, even before the liver is grossly enlarged. Experience at The Mayo Clinic has also served to establish the value of this type of test in surgery of the large bowel.[2] Additional experience with the bromsulphalein test in malignant conditions of the abdomen has led us to place much confidence in its value for detecting hepatic invasion by metastatic tumors and thus to avoid needless surgical intervention. The information obtained by it is not always sufficiently conclusive to warrant a decision on this point alone but in doubtful or borderline cases it is exceedingly important.

SUMMARY

A consideration of the various types of tests for hepatic function indicates that they fall into the first two classifications which have been listed. That is, by revealing hepatic disease, they serve to establish or confirm the diagnosis, or else they warn of operative or postoperative complications. As such they are of great value to the surgeon. There is at present no single test that gives an adequate index to the operative risk in all groups of cases. A consideration of our present knowledge of the physiologic activities of the liver indicates the difficulty in seeking for such a test. It is to be hoped that future studies will permit advances in this field.

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SURGERY IN THE PRESENCE OF DIABETES*

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IN COMPARING the mortality rate from operations on diabetic individuals in the preinsulin era with that in the present day, several factors must be taken into consideration: (1) In the preinsulin era usually only major operations were performed on diabetic patients; (2) operation was usually performed as a last resort; (3) ether or chloroform anesthesia was used; (4) the proper postoperative care of a diabetic patient was not understood as it is today.

In Table I is shown a summary of statistics from the preinsulin era in which the mortality figures range as high as 80 per cent. On the other hand, in some cases the rate is as low as 7.1 per cent which compares very favorably with the rate in the present era. This variation can be accounted for by any of the following factors: (1) the degree of severity of the patient's diabetic condition at the time of operation; (2) his age and general physical condition; (3) pre- and postoperative medical care. The 80 per cent mortality rate

Table I

The Mortality of Operation in the Presence of Diabetes in the Preinsulin Era

	Year	No. of operations	Mortality per cent
Berkman	1915	26	7.6
Binney	1916-1923	32	19
Bruce	1914	--	50
Bruce	1927	4	0
Chovannez	1925	--	40
Cumston	1914	6	16.66
Fisher	1914	86	48.4
Fitz	1918	45	30
Foster	1925	--	45
Gardiner	1922	25 (Amputations)	80
Jones	1923	8	25
Joslin	to 1917	27	18
Joslin	1919	61	9
Karewski	1914	68	11.8
Lahey	1916	14	7.1 (Thyroid)
Mason	1916-1924	101	18
Mayer	1914	--	54.6
Menninger	1925	47	42.5
Morrison	1896-1913	775	23
Mugind	1921	5	80
Noble	1903	--	24
Phillips / Phillips	1902	101	27
Pilcher	1910	--	50 (Amputations)
Strouse	1916	38	31
Tuffier	1914	--	40
Weeden	1897-1922	160	36.8
Young	1918-1922	99	16.1
		Total 1728	Average 31.3

*From Cleveland Clinic.

was for amputations which were performed, of course, in the case of elderly patients with marked arteriosclerosis in whom resistance was naturally low before operation was performed, while the cases in which the operative mortality was low were usually thyroid cases, the surgical risk of which, in the hands of a good surgeon, is not so great, especially in the case of young patients.

According to Table I the average surgical mortality in the preinsulin era was 31.3 per cent as compared with 12 per cent in the present era as shown in Table II. Thus, where formerly three diabetic patients died as the result of operation, now only one dies, showing a very definite decrease, in less than a decade, in the mortality rate.

TABLE II

SURGERY IN DIABETES IN THE INSULIN ERA

	YEAR	NO. OF OPERATIONS	MORTALITY PER CENT
Adams and Wilder	1924	327	1.2
Bauman	1925	56	26.7
Bazin	1930	73	2.7
Bruce	1927	97	2.1
Cohen	1923	8	14
Coler and March	1925	65	24.6
Eliason and Wright	1926	55	41.8
Foster	1925	103	11.6
John	1921-1925	35	8.5
John	1925-1928	276	4.3
John	to 12/5/30 (unpublished)	462	4.7
Joslin	1923	69	5.7
Joslin	1924	75	14.6
Joslin	1925	97	10.3
Joslin	1926	81	14.8
Joslin	1927	321	11.5
Judd	1926	667	3
Lemann	1926	43	2.3
Mason	1925	101	17.8
McKittrick and Root	1928	80	11.2
Menninger	1925	22	4.5
Petty	1924	31	12.6
Rabinovitch*	1930	130	5.3
Reed	1929	43	25.5
Roth	1926	20	10
Weeden	1924	12	1.2
Wilder	1924	327	
		Total 3676	Average 12

*Verbal report.

"Every other diabetic becomes a surgical diabetic before he dies," according to Joslin. Bazin reports that among 221 diabetics admitted to the Montreal hospital in 1929, 87, or 39.3 per cent, were or became surgical cases. In the Cleveland Clinic in a series of 3500 cases of diabetes operation was performed in 762 cases or 21.7 per cent (see Table III). In view of these statistics, diabetic patients present an important problem to the surgeon, for they constitute a large group of his surgical cases. Therefore, surgeons are taking a greater interest in the medical care of diabetics both before and after operation.

For the purpose of discussion our operations on diabetic patients may be divided into two groups: (1) nonemergency operations; (2) emergency opera-

TABLE III

OPERATIONS PERFORMED ON DIABETIC PATIENTS IN THE CLEVELAND CLINIC HOSPITAL FROM THE BEGINNING OF INSULIN ERA

OPERATIONS	NO. OF PATIENTS	DIED	PER CENT
Thyroidectomy	282	19	6.5
Leg amputation	31	4	13
Closure urinary fistula	1	0	
Prostatectomy	48	5	10
Osteoplastic flap	1	0	
Resection tumor of bladder	5	1	20
Dilatation and curettage and radium	7	0	
Fistula and anus-resection	2	0	
Laryngectomy	1	1	100
Plastic operation on neck	1	0	
Carbuncle resection	9	2	22
Appendectomy	8	2	25
Colostomy	4	1	25
Nephrectomy	8	0	
Gall bladder operation	18	0	
Gastric resection	1	1	100
Fracture reduction	4	0	
Resection of rib	2	1	50
Sympathectomy	1	0	
Exploratory laparotomy	26	8	31
Breast amputation	11	1	9
Bone graft	1	0	
Adrenalectomy	4	1	25
Amputation fingers	1	0	
Amputation cervix uteri	1	1	100
Hernia	8	0	
Hydrocele	1	0	
Hysterectomy	10	1	10
Resection tongue for cancer	1	0	
Ligation femoral artery	1	0	
Litholapaxy	1	0	
Resection rectum	7	2	29
Pelviolithotomy, cysts	2	0	
Tracheotomy	1	0	
Drainage parotid abscess	1	1	100
Excision of axillary glands	1	0	
Jejunal fistula	1	0	
Epididectomy	1	0	
Ureter obstruction	1	0	
Resection colon and cecum	3	2	67
Cystectomy	1	0	
Gasserian ganglion resection	1	0	
Gastroenterostomy	1	0	
Injection prostate	1	0	
Mastoidectomy	4	0	
Glands of neck excision	1	0	
Denervation adrenal	7	1	14
Cesarean section	2	0	
Delivery	2	0	
Abscess on scalp	1	0	
Ligation (thyroid)	64	0	
Cystotomy	2	0	
Tonsillectomy	47	1	2.1
Antrum operation	6	0	
Radium implantation	2	0	
Amputation toes	16	0	
Suprapubic puncture	6	1	17
Incision and drainage abscess	32	1	3
Fissure in anus	3	0	
Alcohol injection fifth nerve	1	0	
Blood transfusion	6	0	
Nasal polyps or septum	6	0	

TABLE III—CONT'D

OPERATIONS	NO. OF PATIENTS	DIED	PER CENT
Cataracts resected or lenses	13	0	
Excision moles	1	0	
Prostatic puncture	3	0	
Bursa resection	2	0	
Lacrymal sac resection	1	0	
Circumcision	1	0	
Closure rectal wound	1	0	
Cauterization lip	1	0	
Urethrotomy	1	0	
Ischiorectal abscess incision	2	0	
Hemorrhoidectomy	1	0	
Skin graft	1	0	
Dilatation and curettage	2	0	
Perineal repair	1	0	
Lipoma resection	1	0	
Total number of operations	762		
Total number of deaths	58		
Gross mortality, per cent	7.6		
Net mortality, per cent	5.8*		

*By net mortality we mean elimination of deaths due to other nonsurgical causes.

tions. The first group comprises operations in cases in which the operation can be performed at leisure, that is, when the patient is ready for it. Thus, he can be kept under medical control, and a normal or near normal status can be reestablished by controlling hyperglycemia, by eliminating glycosuria or reducing it to a negligible amount, by compensating for the condition of acidosis, and by restocking the liver and musculature with glycogen. With these precautions, the diabetic patient can undergo an operation with no greater risk than is incurred by the nondiabetic individual. In order to bring about the desired preoperative condition, the patient is placed on a reasonable diet consisting of at least 100 gm. of actual carbohydrates (not total available glucose), 60 to 80 gm. of protein and enough fat to make up a total of 1800 to 2500 calories, depending upon the individual. If he is markedly emaciated, 2500 calories should be given with enough insulin to insure the storage and utilization of the diet. If he is obese, then 1800 or even 1600 calories will be sufficient, including the above-stated carbohydrate-protein allowance. Thus he is made to burn up his superfluous stores of fat and thereby improve his general condition, rendering him less liable to acidosis. If 100 gm. of carbohydrate are utilized in such a diet, and the glycosuria is eliminated or reduced to a negligible quantity in a twenty-four hour specimen of urine, no attention need be paid to the ketoantiketogenic ratios which have received so much attention in recent years.

Now, as to the use of insulin. Almost any diabetic condition can be controlled by the readjustment of diet alone. In mild cases the procedure is simple, namely, the substitution of fats for part of the carbohydrates. The severely diabetic patient fares poorly, however, for the reduction in his diet has to be adapted to the amount of available endogenous insulin which he has at his disposal. Since this amount is very small the patient has to exist on a practically starvation diet in order to keep him sugar-free and control hyperglycemia. This procedure, which was followed in the preinsulin era,

simply amounted to gradual starvation, and it seemed at times as if it were hardly worth the effort. Today this type of individual lives comfortably on a reasonable diet plus insulin and is able to work and to take care of his family.

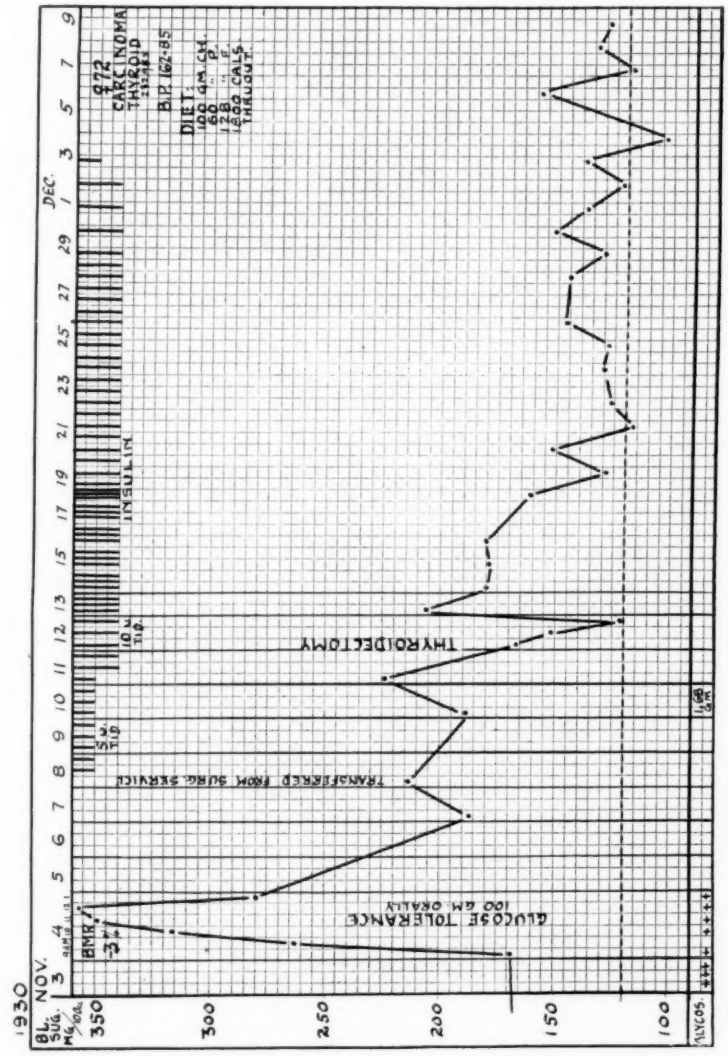

Chart 1.—Chart illustrating the progress of a case of carcinoma of the thyroid associated with diabetes mellitus, before and after thyroidectomy.

The treatment of the surgical diabetic is exactly the same as that of the ordinary diabetic individual—that is, dietary control or dietary control plus insulin until he is ready to be operated upon.

The following case illustrates the regimen which is followed in the usual care of diabetes in preparation for opeation:

A woman, seventy-two years of age, came to the clinic with a malignant condition of the thyroid gland involving the cervical glands on the left side.

There had been a rapid enlargement of the thyroid gland for the preceding six weeks, causing much pain, choking sensations, and hoarseness. There was no loss of weight, tachycardia, or nervousness. Glycosuria had been discovered several years previously but had been easily controlled. At that time she had had some frequency of urination. The weight was normal, the blood pressure was 162/85, the basal metabolic rate was minus 3 per cent. Wassermann was negative. Uranalysis showed heavy glycosuria and a faint trace of albumin. The fasting blood sugar was 169 mg. per 100 c.c. (see Chart 1, Nov. 4, 1930). Thus, in this case a patient in whom diabetes had been present for several years required a major operation. A glucose tolerance test made November 4 showed a frankly diabetic condition and four days later

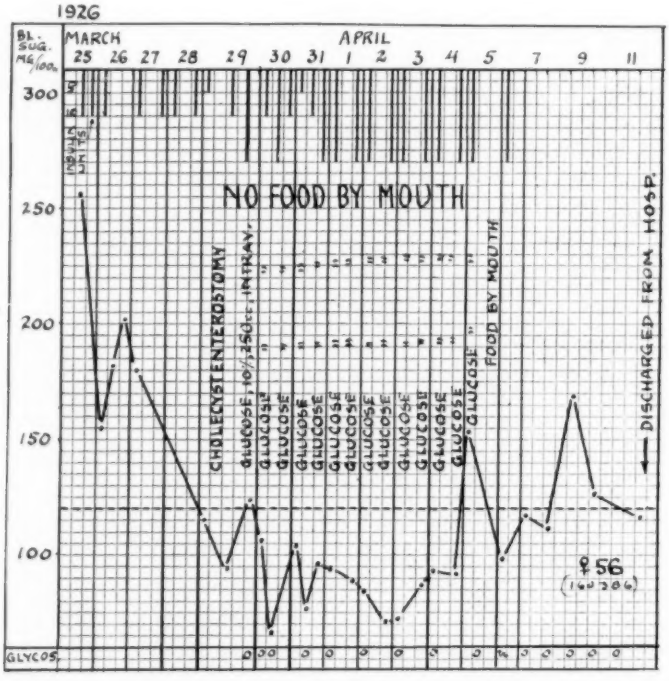

Chart 2.—Chart illustrating the progress of a case of jaundice associated with diabetes mellitus before and after operation; no food was given by mouth for seven days.

the patient was transferred to the diabetic service for treatment. In view of the findings it seemed that we had to deal with an uncomplicated case of diabetes. The patient had no hyperthyroidism and only slight arteriosclerosis. The blood urea was 27 mg. per 100 c.c., uric acid 1.8, creatinine, 1.0, which eliminated the question of nitrogen retention.

The patient was placed on a liberal diet consisting of carbohydrate 100 gm., protein 60 gm., fat 128 gm., a total of 1800 calories. In order to shorten the preoperative period and to ascertain the patient's reaction to insulin in case of an emergency, she was placed on 5 units of insulin t.i.d., the dose being increased three days later to 10 units t.i.d. She showed no reaction and the level of the blood sugar and of the urine sugar was lowered. This routine was also carried out on the day of operation. Following the opera-

tion, the patient was given a saline infusion of 2000 c.c. She made an uneventful recovery and twenty-two days later the use of insulin was discontinued. In the interval following operation the dosage of insulin had been reduced to ten units morning and evening, later to ten units once a day, and then to five units daily. With this dosage the blood sugar remained at almost a normal level and the urine was sugar-free.

A second case, which is summarized in Chart 2, illustrates a somewhat complicated postoperative procedure. A woman, fifty-six years of age, came to the clinic December 16, 1925, with the following history: Diabetes had been discovered sixteen months previously and she had been treated by dietary control and insulin. A few months later intense jaundice developed which cleared up after six months. In December, 1924, the patient was again admitted to the same hospital because of diabetes and jaundice. She had lost 17 pounds in weight in ten days. At the time she was discharged from the hospital she was taking twenty units of insulin daily and was having insulin reactions. At the last examination her blood-sugar content was 300 mg. per 100 c.c.

When she first came to the clinic, December 16, 1925, her weight was 107 pounds (she had been 38 per cent overweight, and now was 16 per cent underweight). Her blood-sugar level was 340 mg. per 100 c.c., urea 36, no plasma acetone. Glycosuria was three-plus, no urine acetone. Subsequent blood-sugar examinations up to the time of her operation for obstructive jaundice gave the following data (Table IV):

TABLE IV

	1925				1926			
	12-16		12-30	12-31	1-1	1-2	1-3	1-4
Blood sugar	7 A.M.			116	92	126	75	107
	12 noon	340 (2 hr.)	106	81	132	110	112	
	5 P.M.		58	114	95	81	88	
Units insulin	20		10	10	Discontinued			

It was clear that this patient had been getting too much insulin previous to her entering the clinic, for each dose of 20 units before she came in produced a reaction. During her week's stay in the hospital prior to her operation she was running a normal blood sugar morning, noon and evening, even after insulin was discontinued, which indicated that she required no insulin at this time. On January 18, 1926, a glucose tolerance test was made with the following result (Table V):

TABLE V

	FASTING	½ HR.	1 HR.	2 HR.	3 HR.	4 HR.
Blood sugar	145	272	434	440	333	199
Glycosuria	neg.		3-plus	3-plus	3-plus	1-plus

This test showed that we were dealing with a comparatively mild but a definite case of diabetes which required watching, for while the hyperglycemia was controlled during the day on a regulated diet, yet after a heavy glucose meal the patient would have a heavy and prolonged hyperglycemia.

On March 25, 1926, she entered the hospital for a gall bladder operation. On a routine diabetic diet and ten units of insulin twice a day the hyperglycemia, which had reappeared, subsided in a few days and she was operated upon. No stones were found but the common duct was found to be very thick and hard, causing obstruction, consequently a cholecystduodenostomy was performed. The pancreas was palpated and was found to be freely movable, somewhat nodular, and very hard.

On the morning of the operation the patient's blood-sugar content was 115 and she was given five units of insulin before the operation. The noon blood sugar was 94 and at this time ten units of insulin were given. At 2:20 P.M. the blood sugar was 123, and she was given twenty units of insulin and 250 c.c. of 10 per cent glucose solution intravenously.

Here, then, was a case in which all food and drink by mouth had to be withheld in order to avoid peristalsis in a freshly operated gut. The patient received 250 c.c. of 10 per cent glucose intravenously night and morning for a week. In addition, she received 1200 c.c. of 5 per cent glucose by rectum, b.i.d. The patient made an uneventful recovery and on the seventh day following operation she was given food by mouth.

Insulin was given for one more day after which it was discontinued, and with the exception of one day the blood-sugar level was normal. On the fourteenth day following her operation, the patient was discharged with a normal blood sugar. A letter received on December 31, 1930, stated that she was well, working, and taking five units of insulin three times a week.

This case differs from the previous one in that nourishment could not be administered by mouth and therefore had to be given intravenously and by rectum. In any case in which nourishment cannot be given by mouth postoperatively, whether to a diabetic or to a nondiabetic patient, I know of no better method than to give glucose intravenously. The above case demonstrates that this method can be used safely in the case of a diabetic patient, provided that enough insulin is used to prevent hyperglycemia. In this way the possibility of acidosis following operation is automatically eliminated.

It is well known that the use of intravenous glucose following operation, and glucose or carbohydrate in some form on the night preceding operation, is a very valuable measure, especially if the patient, on account of incessant vomiting, becomes partly dehydrated, with resulting alkalosis which in turn aggravates the vomiting, thus establishing a vicious circle. In the case of a diabetic patient, such a situation can arise from acidosis. By the use of glucose solution plus insulin, administered intravenously, the vicious circle is broken and the patient has an infinitely better chance of recovery.

The question arises—can glucose be given safely to diabetic patients with the same result as in the case of a nondiabetic patient?

While the normal individual apparently has available an unlimited supply of endogenous insulin, so that no matter how much carbohydrate he is given he can take care of it, the diabetic patient, on the other hand, has not enough endogenous insulin available to take care of the carbohydrates. If the use of glucose in the case of a nondiabetic individual is a good physiologic measure, it should be equally good in the case of a diabetic individual pro-

vided we can help him to take care of the added glucose in the blood stream. In the preinsulin era this was impossible, for any addition of glucose to the already increased amount of sugar in the blood would have been an unsafe procedure. However, since the advent of insulin, the problem has taken on an entirely different aspect. The needed insulin can be supplied from without and the operative mortality in diabetic patients can be lowered.

In Fig. 1 is shown the method which I use in the clinic for administering glucose intravenously. The glucose apparatus should first be filled to the tip with the solution which should be quite warm in order to allow for cooling.

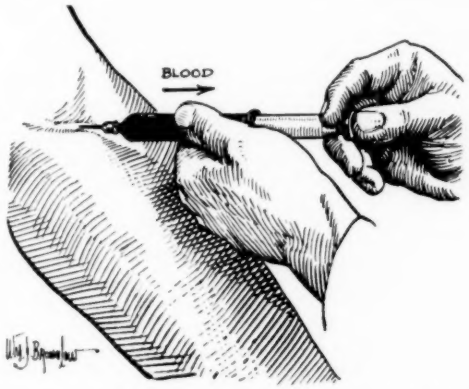

Fig. 1.—Drawing showing combined technic of administering insulin (intravenously) and securing blood through one venipuncture.

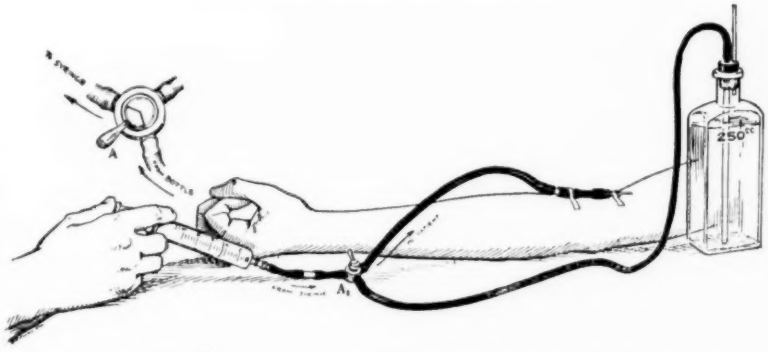

Fig. 2.—Drawing illustrating a simple, inexpensive and efficient outfit for the intravenous administration of glucose.

A specimen of blood is secured through a venipuncture for blood-sugar determination. While the needle is still in the vein, the end of the needle next to the syringe should be grasped with a hemostat so as not to dislodge the needle from the vein, and the glucose outfit connected. In this manner blood is secured and glucose administered through one venipuncture. A practical and simple outfit for the administration of glucose is illustrated in Fig. 2. This consists of an ordinary bottle with a capacity of 250 c.c. (8 ounces), rubber tubing, and a three-way stopcock. By one motion the syringe is filled from the bottle, by another the contents are emptied into the blood stream, this procedure being repeated until all the solution has been used. If a

16-18 gauge needle three-quarters of an inch long, is used, the time required for the administration of glucose should not be more than ten minutes. The addition of 250 c.c. of the solution to the circulating blood volume represents an increase of about 5 per cent.

The preparation of glucose solution is simple. Twenty-five gm. (1 ounce) of chemically pure glucose is dissolved in an Erlenmeyer flask in enough freshly distilled water to make a solution of 250 c.c. This is brought to the boiling point. The neck of another Erlenmeyer flask is sterilized in a beaker of water and the dissolved glucose is filtered from the first flask to the sec-

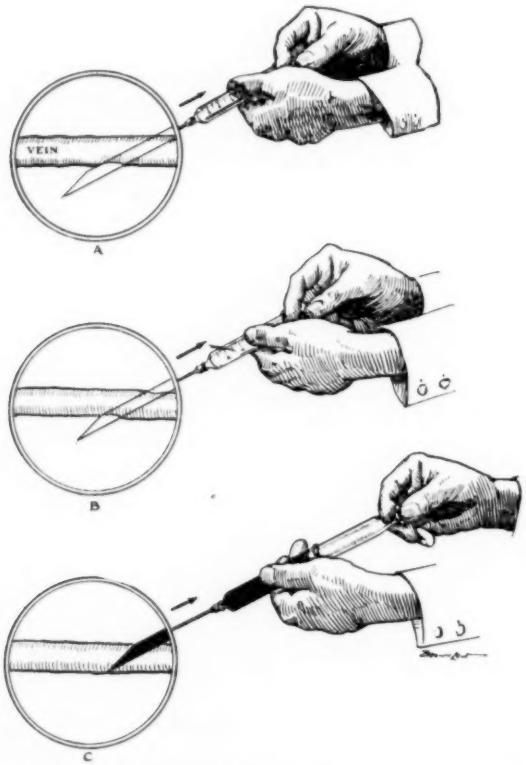

Fig. 3.—(*a*) and (*b*). Drawings illustrating a possible accident in making a venipuncture. (*c*) Drawing illustrating a method of preventing such an accident.

ond flask. The contents are simply brought to the boiling point and then the solution is sterile and ready for use.

It may be difficult to make the venipuncture. Since the needle is necessarily quite sharp, it may perforate both walls of the vein and Fig. 3 illustrates a method for preventing such a mishap. Simply pull slowly on the syringe and plunger at the same time, and as soon as the needle has entered the vein, blood will appear in the syringe.

When enough insulin has been added to the glucose, the diabetic patient, theoretically, is protected from a rise in blood sugar. That this is actually the case in practically all instances is demonstrated in Table VI

which shows a summary of the fall or rise of the blood sugar following the intravenous administration of glucose plus insulin in a series of 54 cases of diabetes. The findings in this table show clearly that there need be no fear of endangering the status of a diabetic patient by the administration of glucose if the blood sugar is checked subsequently. This series of cases has been collected from data secured in cases of diabetes in which an operation has been performed and in cases of diabetic coma, in which also the use of glucose intravenously with insulin is a great aid in overcoming acidosis and increasing the excretion of acetone bodies through the urine. Furthermore, by this procedure the practically glycogen-free liver, as well as the heart muscle, is restocked with glycogen.

TABLE VI

CHANGES IN BLOOD SUGAR AFTER THE INTRAVENOUS ADMINISTRATION OF GLUCOSE—FIFTY-FOUR CASES

	CHANGES IN BLOOD SUGAR MG. PER HR.				CHANGES IN BLOOD SUGAR MG. PER HR.			
CASE	FALL	NO CHANGE	RISE		CASE	FALL	NO CHANGE	RISE
1	22	--	--		28	--	--	22
2	24	--	--		29	--	--	14
3	60	--	--		30	28	--	--
4	33	--	--		31	25	--	--
5	19	--	--		32	11	--	--
6	38	--	--		33	10	--	--
7	28	--	--		34	8	--	--
8	34	--	--		35	14	--	--
9	10	--	--		36	208	--	--
10	26	--	--		37	6	--	--
11	47	--	--		38	3	--	--
12	--	--	38		39	--	--	5
13	--	--	18		40	4	--	--
14	39	--	--		41	4	--	--
15	58	--	--		42	9	--	--
16	24	--	--		43	18	--	--
17	18	--	--		44	22	--	--
18	--	0	--		45	--	--	0.3
19	--	0	--		46	38	--	--
20	28	--	--		47	50	--	--
21	34	--	--		48	24	--	--
22	10	--	--		49	16	--	--
23	26	--	--		50	22	--	--
24	47	--	--		51	28	--	--
25	--	--	38		52	61	--	--
26	--	--	20		53	33	--	--
27	1.8	--	--		54	19	--	--
					54	1287.8	0	155.3

Of a total of 54 cases, 44, or 81.5 per cent, showed a fall of blood sugar; 2, or 3.7 per cent, showed no change; and 8, or 14.8 per cent, showed a rise of blood sugar. The average fall of blood sugar (44 cases, or 81.5 per cent) was 29 mg. per hour; the average rise of blood sugar (8 cases, or 14.8 per cent) was 19 mg. per hour.

Now, as to the procedure in cases of emergency operations on diabetic patients. Of course, the operation is the first consideration. However, much can be done during the half hour or so in which the patient is being prepared for operation. If the picture is one of clear-cut diabetes, if the patient has an acetone breath and signs of acidosis, then through one venipuncture 10 units of insulin can be administered and 6 to 8 c.c. of blood withdrawn

(see Fig. 1). In from twenty to twenty-five minutes the blood-sugar reading can be obtained, the plasma acetone and CO_2 determined, and later the blood urea. If the blood-sugar level is high, the plasma acetone heavy, the CO_2 low or lowered, then another ten units of insulin may be given hypodermically while the patient is on the operating table (a half hour after the first administration) and another ten units at the end of the next half hour. As soon as the patient is back in bed, glucose plus insulin should be administered intravenously and large doses of saline solution (3000 c.c.) should be given by hypodermoclysis, and repeated after from four to six hours. The blood sugar should be checked hourly or bi-hourly in order to give the patient the maximum amount of protection. If biochemical data cannot be obtained then we must depend upon the data obtained by uranalysis. If too much insulin has been given, 5 to 10 c.c. of 50 per cent glucose (obtainable in sterile ampules) given intravenously quickly compensates for the

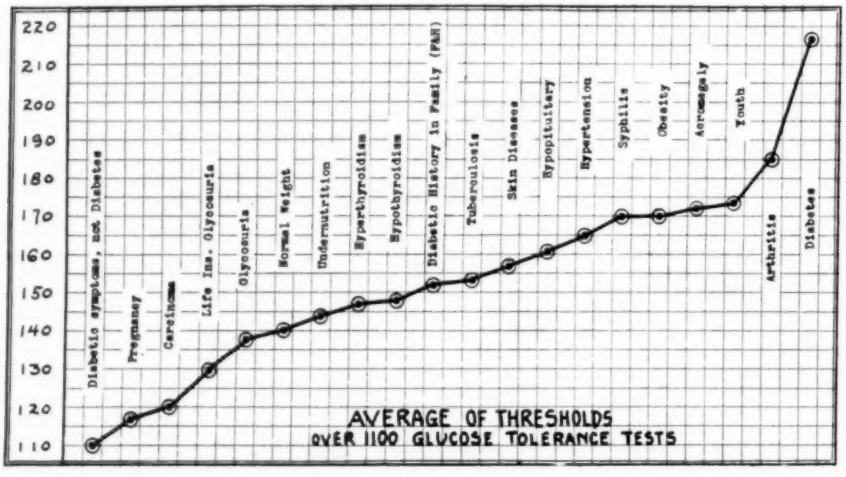

Chart 3.—Chart showing the average renal threshold in various diseases in 1100 glucose tolerance tests.

hypoglycemia. The important point is to be constantly on the watch in order to bring the patient to safety.

If time permits before the operation, 250 c.c. of 10 per cent glucose may be given intravenously with 20 units of insulin, for this will help to restock the liver with glycogen and strengthen the heart. We must remember that 250 c.c. of 10 per cent glucose represents but 25 gm. of glucose; theoretically 8 to 10 units of insulin ought to be sufficient to burn up this amount, and as the carbohydrate burns, the ketone bodies burn as well. The added liquid also increases diuresis which washes out more ketone bodies.

If any infection is present a blood culture should be made before operation and if bacteremia is found to exist then a death following operation is not a surgical death. A second blood culture should be made twenty-four to forty-eight hours after operation in order to ascertain whether bacteremia has developed. This measure protects both the surgeon and the physician and aids in making the prognosis.

GLYCOSURIA

Glycosuria, when discovered in any surgical case, should never be disregarded. It may be due only to a low renal threshold, but on the other hand, it may be the first sign of frank diabetes. The answer to the question as to whether the glycosuria is diabetic or nondiabetic depends on two individual factors: (1) the concentration of sugar in the blood, and (2) the height of the renal threshold. The problem of diagnosis can only be solved by blood-sugar studies.

In a series of 337 cases of ambulatory patients with glycosuria, subjected to a glucose tolerance test, we found that in 63 per cent the glycosuria was of the nondiabetic type, and in 37 per cent it was of the diabetic type. The reverse was found to be true in 239 cases of glycosuria associated with hyperthyroidism—namely, in 36 per cent the glycosuria was of the nondiabetic type, and in 63 per cent it was of the diabetic type (see Table VII).

In an analysis of a series of 1100 glucose tolerance tests it was found that the renal threshold varied from 110 to 212 mg. per 100 c.c. These figures represent only the average renal threshold in each type of condition (see Chart 3).

Transient glycosuria is not a phantom but a real clinical entity and should always be taken into consideration.

GLYCOSURIA IN GALL BLADDER DISEASE

In a group of 6 cases of gall bladder disease (cholecystitis and cholelithiasis) in which a glucose tolerance test was made, 2 patients showed glycosuria, 4 no glycosuria; 5 showed some degree of hyperglycemia, and one showed no hyperglycemia. These findings show that the blood-sugar level is a keener laboratory evidence than is the finding of glycosuria for in this group we find glycosuria in 33 per cent whereas 83 per cent of the cases in the same group present hyperglycemia. When we went deeper into the question and made a glucose tolerance test for the purpose of a differential diagnosis, we found that 50 per cent of the group had a definite diabetic curve and 50 per cent a normal curve. Of this latter group two patients were operated upon and the rest were treated medically. In a total of 17 cholecystectomy operations or cholecystotomy operations performed in the Clinic on diabetic patients since 1921, there has been no death.

ANESTHESIA IN DIABETES

The use of chloroform as a general anesthetic was discarded in this country about thirty years ago. In cases of diabetes it is contraindicated because it causes hyperglycemia (Blum) and is likely to produce acidosis which leads to coma. It is also injurious to the liver.

Ether is of very little value as an anesthetic although it is necessary in some instances. However, its use is avoided in operations on diabetic patients on account of the danger of postoperative nausea. The Mayo Clinic, however, reports some excellent results from the use of ether. Bloor found from experiments on animals that ether produces a rise of fat content in the

TABLE VII

FINDINGS IN 1100 GLUCOSE TOLERANCE TESTS

THE FOLLOWING FINDINGS	TYPE OF CURVE			RENAL THRESHOLD			BLOOD PRESSURE			RELATION OF FLUID INTAKE TO OUTPUT		
	TOTAL CASES	NON-DIABETIC PER CENT	DIABETIC PER CENT	TOTAL CASES	180 AND BELOW PER CENT	ABOVE 180 PER CENT	TOTAL CASES	140 OR BELOW PER CENT	ABOVE 140 PER CENT	TOTAL CASES	OUTPUT LESS THAN INTAKE PER CENT	OUTPUT MORE THAN INTAKE PER CENT
All cases of glycosuria	337	63.0	37.0	162	85.8	14.2	82	85.3	14.7	198	79.7	18.5
Glycosuria discovered during our examination	138	66.0	33.0									
Glycosuria discovered previous to our examination	199	60.3	39.6									
Glycosuria found in life insurance examination	61	62.2	37.7	54	89.0	11.0	17	94.1	5.8	61	88.2	11.2
Hyperglycemia found on routine examination	65	60.0	40.0							62	93.4	6.4
Diabetic history in family (F. & H.)	104	44.2	55.7	58	75.8	24.1	51	60.7	39.2	90	70.6	25.3
Obesity (46 per cent male—54 per cent female)	172	34.3	65.6	100	54.0	46.0	120	57.5	42.5	114	80.5	18.6
Normal weight	287	74.2	25.8	31	83.8	16.2	62	80.6	19.4	283	82.8	16.0
Undernutrition	171	79.0	21.0	105	80.0	20.0	102	80.0	20.0	170	78.7	19.4
Hyperthyroidism (29 per cent male—54 per cent female)	239	36.3	63.5	180	81.1	18.9	235	42.9	57.1	286	72.6	23.3
Hypothyroidism	9	89.0	11.0	5	100.0		8	100.0		9	77.7	22.2
Acromegaly	6	50.0	50.0	4	50.0	50.0	5	80.0	20.0	6	100.0	
Hypopituitarism	33	91.0	9.0	11	63.6	36.3	14	85.7	14.2	32	71.7	24.9
Hypertension	61	37.7	62.2	49	65.3	34.7	60	100.0		61	73.5	26.0
Pregnancy (glycosuria)	21	57.1	42.8	17	94.1	5.9				21	81.1	14.2
Tuberculosis	8	62.5	37.5	6	66.0	34.0	6	100.0		8	62.5	12.5
Arthritis	17	52.9	47.0	9	55.0	45.0	10	100.0		17	88.3	11.8
Carcinoma	6	16.6	83.3	4	100.0		6	50.0	50.0	6	100.0	
Syphilis	17	41.1	58.8	14	71.5	28.5	11	81.8	18.1	17	82.5	17.7
Skin diseases	20	90.0	10.0	9	66.6	33.3	12	75.0	25.0	20	90.0	10.0
Patients under 20 years	77	70.0	29.9	33	63.6	36.3	30	86.6	13.3	77	78.0	22.0
Diabetes				54	27.7	72.2	33	66.6	33.3	335	78.2	17.1
Diabetic symptoms—not diabetic				13	100.0		9	100.0		30	66.1	33.0

blood during narcosis, this rise continuing during the anesthesia until death occurs. Such a lipemia naturally predisposes to acidosis. Van Slyke, Austin and Cullen also report the development of true acidosis following ether anesthesia.

Nitrous oxide which is used almost generally in the Cleveland Clinic, stands out preeminently, we believe, as the anesthetic of choice. Ethylene is a good type of anesthetic and is used successfully in various sections of this country.

Local and lumbar anesthesia are coming into more and more frequent use and we believe these methods have much to offer if used in experienced

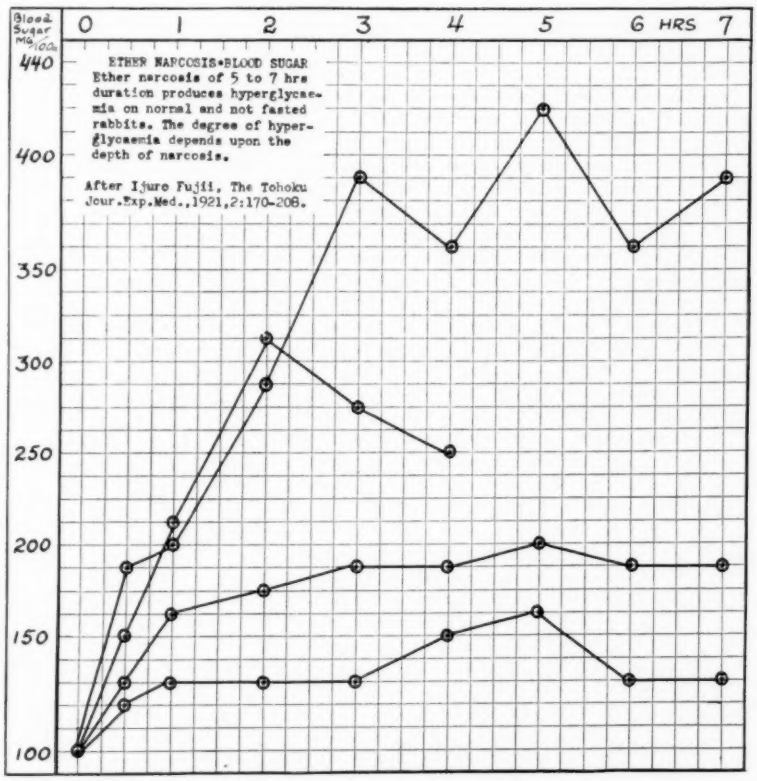

Chart 4.—Chart showing blood-sugar studies in ether narcosis in rabbits. (After Fujii.)

hands. Lumbar anesthesia is especially to be recommended in operations on the lower extremities and in the case of elderly patients.

We must bear in mind that any anesthetic which is apt to cause vomiting is injurious to the patient, dissipating his energy, and causing alkalosis and a degree of starvation which results in acidosis, as shown by Haden and Orr. Sodium chloride is indicated in all cases of vomiting in order to replace the lost hydrochloric acid in the stomach.

The effect of ether anesthesia on the blood sugar is illustrated in Chart 4, and Table VIII presents data obtained from operations on human subjects, in which general anesthetics were used.

BLOOD TRANSFUSION

There is perhaps no better single helpful measure in postoperative complications than blood transfusion, and it should be used early. Transfusion is indicated in the following instances: (1) reduced blood volume (loss of blood, hemorrhage) as indicated by low red blood count, low hemoglobin; (2) in all infections, when repeated, transfusions of 250 c.c. should be given before and after operation; (3) in cases which present bad surgical risks, such as carcinoma of the rectum or breast, gastroenterostomy, etc. It is well to remember, also, as pointed out by Staub, that if the donor has eaten a heavy carbohydrate meal from four to seven hours previous to the transfusion, his blood has an action resembling that of insulin.

TABLE VIII

THE EFFECT OF GENERAL ANESTHETICS ON BLOOD SUGAR
(John)

OPERATION	BLOOD SUGAR BEFORE OPERATION	BLOOD SUGAR AFTER OPERATION	PER CENT OF INCREASE	PER CENT OF DECREASE
Massive resection for carcinoma of pancreas, colon, and stomach	182	395	117	--
Gall bladder drainage	131	143	9	--
Lobectomy	78	147	89	--
Thyroidectomy	88	98	11	--
Thyroidectomy	84	109	29	--
Thyroidectomy	106	118	11	--
Thyroidectomy	133	168	26	--
Thyroidectomy	155	193	27	--
Thyroidectomy	76	89	17	--
Tonsillectomy	303	434	43	--
Tonsillectomy	95	89		6
Hemorrhoidectomy	97	68		42
Incision of infected thumb	150	139		7

KIDNEY INSUFFICIENCY

In cases of kidney insufficiency as manifested by a high blood urea, uric acid and creatinine, without edema or when only slight edema is present, it is well to rely on saline infusions (3000 c.c. each time) and on glucose given intravenously. High metabolites in a diabetic usually appear as a result of the concentration of blood (anhydremia) rather than of renal damage, or the combination of the two conditions. This condition usually accompanies acidosis, and as the high blood sugar causes general dehydration of the tissues, the administration of fluids tends to reestablish the normal status.

Table IX illustrates the case of a young man of twenty-six years of age who showed acidosis and a marked oliguria. His urine output was only 375 c.c. the first day and 330 c.c. the second day, as against an intake of 2055 and 2430 c.c. of water. Renal damage was apparently present at the start, his plasma CO_2 being 21.4, blood urea 162-255, creatinine 3.1 to 3.7, uric acid 5.2 and there was no excretion of the phenolsulphonephthalein in two hours. Urine excretion remained low for five days, during which time the CO_2 values continued to be low. We were, therefore, dealing with a condition of acidosis which in spite of large doses of insulin did not clear up. No

TABLE IX

DATE	BLOOD UREA	BLOOD CREATININE	BLOOD U.A.	PHENOLSULPHONEPHTHALEIN	WATER INTAKE URINE OUTPUT	C.C. 10% GLUCOSE	INSULIN UNITS	FISHER'S SOLUTION	CO_2
2/14/25					2055/ 375	1000/4	200		21.4
2/15/25					2430/ 330	500/2	200		31.5
2/16/25	162	3.1	5.2		2560/ 570	250	160		36.6
2/17/25	192	3.7		0/0	2990/ 930		100		44.3
2/18/25					2650/ 870		30		29.0
2/19/25	201				3270/1255		30	500 c.c.	19.5
2/20/25	222				2820/ 965		105		17.6
2/21/25	255				2375/1529		60		23.3
2/22/25	210				2440/2358		60		19.5
2/23/25	204				2800/2900		60		27.1
2/24/25	126				2520/5240		60		23.3
2/25/25	171			5/5	2400/6480		80		32.8
2/26/25	138				1120/3300*		100		29.0
2/27/25	66	2.3					100		44.3
2/28/25	42			15/20			100		55.7
3/ 1/25	51						100		
3/ 2/25	36		1.3				100		44.3
3/ 3/25	57						60		55.7
3/ 4/25	57						60		65.3
3/ 5/25	15	1.3		30/15			60		
3/ 6/25	24						60		63.3
3/ 7/25				50/20			60		
3/18/25	24						60		

*Progressive observations on a case of diabetes with marked oliguria.

doubt the kidneys played their part and the ketones aggravated the renal damage. Five hundred c.c. of Fisher's solution was given intravenously, following which the urine output rose from day to day, until on the sixth day it amounted to 6480 c.c. against the intake of 2400 c.c. of water. The edema which had become marked, began to clear up as did the acidosis. The phenolsulphonephthalein output rose to 5 and 5, the first and second hours respectively, then to 15 and 20 and 30 and 15, and the urea dropped from 255 to 15 on the fifth day of March. The use of insulin alone did not clear up this condition of damaged kindeys; increased intake of water was of no use as the patient was retaining most of it, and the problem was to induce proper elimination through the kidneys in order to enable the patient to excrete the metabolites and the ketone bodies which were circulating and damaging the kidney further, thus keeping up a state of acidosis. The use of Fisher's solution was effective and therefore I think that it has its place in renal therapy.

Another case showing a renal complication was that of a sixty-seven year old physician, who was brought in for prostatectomy. He was in coma when he entered, and showed signs of having lost much weight. His blood pressure was 192/114 and he showed considerable arteriosclerosis. His blood urea was 291 and blood sugar 543.

After the administration of insulin, 80 to 100 units per day in twenty unit doses, and infusions and glucose intravenously, the blood urea level reached normal in seven days, the blood sugar reached a normal level in six days, and the patient was operated upon on the nineteenth day. An uneventful recovery followed. The patient has been carrying on a heavy coun-

try practice ever since and now at the age of seventy-one years, without insulin, which was discontinued on the forty-fourth day, his blood sugar remains nearly normal and his urine sugar-free.

OXYGEN TENT

The postoperative use of the oxygen tent is indicated in cases which show any degree of anoxemia and it should be utilized before the patient becomes definitely cyanotic. The clinical signs of anoxemia are excitability, stimulation, headache, rapid pulse and dusky appearance of the nails. The use of the oxygen tent should be explained to the patient in order to secure his cooperation.

The average case requires an oxygen concentration in the tent of about 45 to 50 per cent (4 to 5 liters per minute). This amount may vary anywhere from 40 to 90 per cent (up to 15 liters of oxygen per minute). Following prolonged general anesthesia the patient should have inhalations of CO_2-O_2 (5 per cent CO_2-95 per cent O_2) three times a day for at least three postoperative days, in order to expand his lungs, to ensure a better aerating surface, and to prevent atelectasis. This procedure should be repeated three to four times daily, for a period of from fifteen to twenty minutes, for it is a great aid in preventing postoperative pneumonia.

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LABORATORY AIDS IN SURGERY OF THE BONES AND JOINTS*

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IN THE past the pathologist in order to carry out his then academic studies was forced to wait upon the treatment by the clinician in order to receive a specimen, or in most cases to abide by an ultimately fatal result before receiving on opportunity to investigate the disease at necropsy. Laboratory studies had little or no direct influence upon either diagnosis or treatment and only added to the practitioner's hindsight rather than to his foresight. Today there is fortunately a reversal in the relationship between the laboratory and the surgeon and the laboratory studies precede rather than follow treatment. More and more the practitioner is availing himself of laboratory aids, in diagnosis and therapy and wisely awaits in many instances the results of these findings before proceeding.

In the realm of bone and joint surgery some of these formerly laboratory procedures have become so indispensable to the clinician that one of these instruments, the x-ray, is now usually included as a matter of clinical routine. In fact a knowledge of when to employ the laboratory and how to interpret the findings resulting from laboratory study, constitutes today the backbone of bone and joint surgery.

In discussing the application of laboratory aids to this field of surgery, it is convenient to divide the subject into the separate divisions of: (I) bacteriologic and serologic studies; (II) roentgenologic diagnosis; (III) pathologic diagnosis and biopsy; (IV) studies of the blood chemistry. While the use of the roentgenogram and the pathologic study of the material obtained at operation apply universally to all the diseases and tumors of the bone, bacterial and serologic studies are assuming an equal value, particularly since the Wassermann reaction has been adopted as routine in medicine and surgery. Blood chemistry studies especially of the calcium and phosphorus content are more recent, but their sphere of clinical usefulness is being rapidly extended.

I. BACTERIOLOGIC AND SEROLOGIC STUDIES

Syphilis.—No study of a bone lesion is complete without the blood Wassermann report and no surgical procedure on a bone other than an emergency, such as a fracture or acute osteomyelitis should be undertaken without awaiting this report. Syphilis of the bone is probably the most protean of all osseous lesions and may simulate osteomyelitis, a benign bone tumor or sarcoma, or a metastatic carcinoma of the bone. It is therefore not unusual for a case which presents in the x-rays the features of a typical sarcoma to prove to be, after complete laboratory studies have been made, syphilitic

*From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

in nature. When such a case is met with and a positive Wassermann report is obtained, in spite of sarcomatous features in the x-rays and the clinical picture, a course of antisyphilitic treatment should be tried before instituting surgery. Improvement of the condition under arsphenamine therapy is practically incontrovertible evidence of syphilis.

Despite this indisputable value of the Wassermann reaction and of arsphenamine treatment, the application of these preliminary tests to the field of bone surgery, particularly when the patient is of good social status, is overlooked in a surprising number of cases. Two instances in which this working rule in the diagnosis and treatment of bone lesions was not applied are reported below, in order to emphasize once more the importance of ruling out syphilis regardless of the clinical impression.

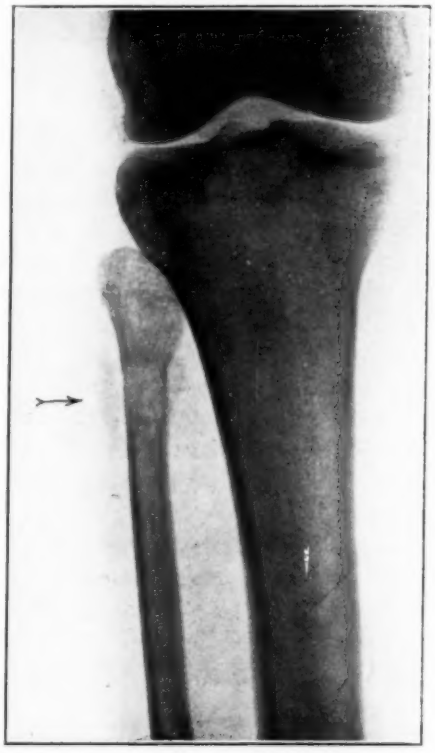

Fig. 1.—Case 1. Roentgenogram showing bone destruction and bone production in a small zone below the head of the fibula in a syphilitic patient, simulating osteogenic sarcoma. This bone was resected for sarcoma without awaiting the Wassermann report. A frozen section was not made because of the ossification present and smears or teasing preparations were omitted at the time of operation.

CASE 1.—The patient was a colored male aged thirty-nine, who gave a history of a penile lesion with a large bubo in the left inguinal region, occurring fifteen years previously. The present illness started with an injury to the left leg two years before, followed in the last two weeks by pain. The pain was dull and intermittent and worse when standing. There was a diffuse swelling in that region.

The general examination was negative except for the slightly enlarged inguinal and axillary lymph nodes. The heart and aorta were slightly enlarged and the liver was palpable one fingerbreadth below the costal margin. Just below the left knee over the region

of the head of the fibula there was slight tenderness and increased sense of resistance. The x-ray of the area (Fig. 1) showed bone destruction and bone production in a small zone below the head of the fibula. The new bone formation simulated a periosteal osteogenic sarcoma.

The patient was bled for Wassermann December 13, 1928, and the operation was performed December 15, 1928. The operative note follows: Resection upper end of left fibula. Through an incision made over the head of the fibula and extending down the outer side of the leg the bone was exposed. There was soft bone formation at this point easily taken out with a curette and part of the bone was removed for frozen section, but the pathologist was unable to make a section because of the amount of bone spicules present. The fibula was almost completely destroyed at one point. It was decided to resect the bone. This was done by first dividing it well down in the leg and dissecting upward to the bone

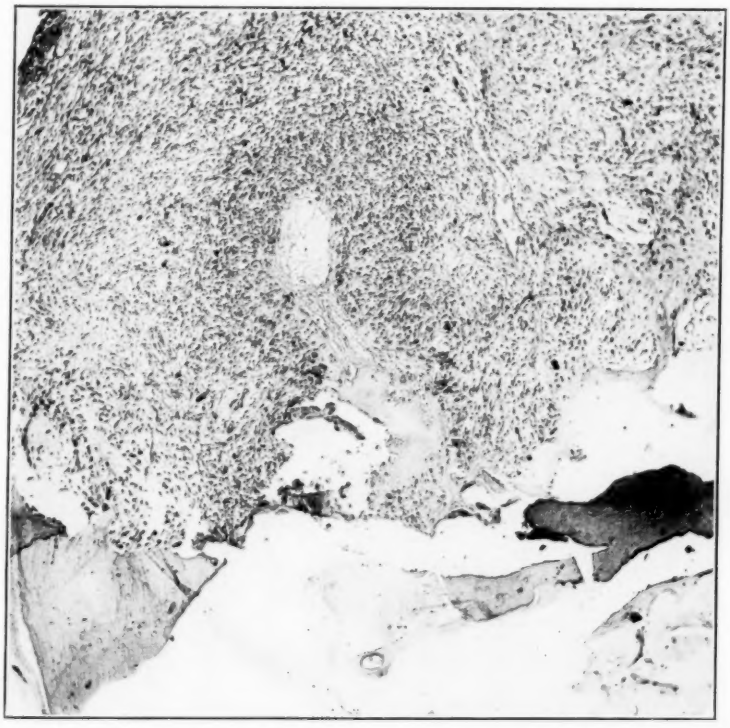

Fig. 2.—Microphotograph from the lesion shown in Fig. 1. The microscopic picture shows perivascular infiltration and wandering cells of the epitheloid type typical of syphilis.

where the branches of the nerve crossed it. The bone was cut across at this point so that the nerves could be retracted around the end and placed posteriorly. The remainder of the bone including the tumor and head of fibula was removed.

At the point of the tumor, the gross specimen showed the shaft of the fibula completely surrounded by a layer of newly formed bone, which also extended into the marrow cavity, obliterating it with newly formed osteoid tissue. The shaft at this point was definitely expanded. At one area in the sectioned bone there was softened material of a dark red color. Under the microscope (Fig. 2) the new bone was of a benign inflammatory type, with perivascular infiltration of lymphocytes and plasma cells. Foci of lymphoid cells were also scattered through the new bone. There was no evidence of malignancy in the section, nor any miliary gummas or definite tubercles. There was, however, a mass of necrotic cartilaginous material occupying the marrow cavity. The healing reaction present overshadowed the signs of inflammation.

The patient recovered from the operation rapidly. The Wassermann reaction was reported as 4-plus the same day as the operation. As soon as he was able to leave the wards he was transferred to the Syphilitic Department for treatment and in that department received therapy from December 27, 1928, until September 9, 1929. Under antisyphilitic treatment the liver decreased in size, but the widened aorta persisted.

Fig. 3.—Case 2. Roentgenogram resembling a Ewing's tumor in a case of congenital syphilis in a white female, aged seven. A resection was performed before the Wassermann report was completed. A frozen section made at the time of the operation revealed dense round cell infiltration which was thought consistent with Ewing's sarcoma. The final sections are shown in Fig. 4.

Comment.—Two errors were made in this case, one from the clinical standpoint in proceeding without the Wassermann report, despite the history of a penile lesion and the other in pathologic technic in not preparing material for microscopic examination by smears or teasing in spite of the ossification present.

CASE 2.—The patient was a white female of seven and one-half years who had always been well with the exception of measles at six and an attack of whooping cough at seven. The present illness began two years ago when the patient fell from a swing, bruising the left lower leg. This incident was forgotten until four months ago, January, 1930, when there was pain along the lateral side of left lower leg, exacerbated by walking. At the same time a swelling appeared over this area which gradually increased in size.

The general physical examination was negative. There was a fusiform symmetrical fullness in the middle third of the left lower leg on the lateral side, which was firm and slightly tender to pressure. It was not attached to skin and the nodes in the groin were not enlarged.

The x-ray (Fig. 3) showed a circular area of bone destruction extending through the cortex of the fibula surmounted by a periosteal reaction which extended on either side, one-half the length of the bone. The operative procedure was carrid out on the basis of clinical

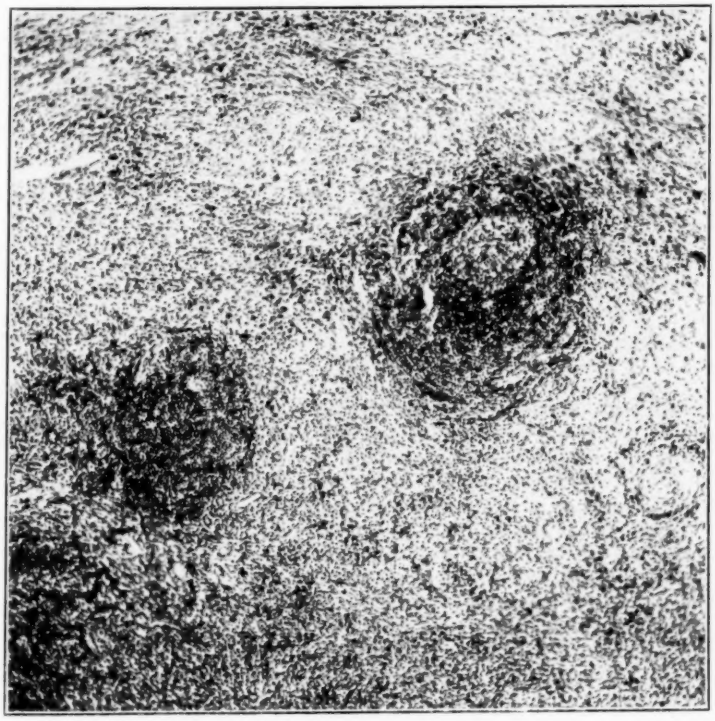

Fig. 4.—Microphotograph of the lesion shown in Fig. 3. The microphotograph shows clearly miliary gummas present amid an area of round cell infiltration and granulation tissue.

data and x-ray only, the interpretation of the x-ray report being that of a Ewing's tumor. The patient was operated upon the same day that the blood was taken for Wassermann reaction. The Wassermann report was 4-plus.

At operation an incision was made over the head of the fibula and carried down through the subcutaneous tissue in order to locate the popliteal nerve. The incision then was carried down the leg a little above the ankle parallel to the fibula, the external popliteal nerve being dissected free. The fibula was freed and cut across two inches below its head and the same distance above the ankle joint.

The gross specimen showed a mass of necrotic and softened fibroid material occupying an expanded portion of the fibula. Most of the expansion was due to new bone formation surrounding the softened center, and at either end of the expanded portion of the fibula the periosteum was raised by reactive new bone. The fibrous structure of a Ewing's tumor was not present. Under the microscope the new bone bordered upon areas of bone de-

struction infiltrated by dense lymphoid tissue. At the frozen section the small islands of hyalinized necrosis present at several points and typical miliary gummas disclosed (Fig. 4) by further sections, were not seen and the microscopic picture was thought consistent with the diagnosis of Ewing's tumor.

The patient made an uneventful recovery from operation and antisyphilitic treatment was started in the hospital. The patient's condition was reported to the family physician who assumed charge of the antisyphilitic treatment. Radium therapy was also advised.

Comment.—This second case emphasizes the point, that while the microscope and x-rays are helpful in the diagnosis of syphilis, neither compare in efficiency and conclusiveness to the Wassermann reaction and a therapeutic test with arsphenamine. In occasional cases the syphilitic lesion under the microscope will show miliary gummas, perivascular infiltration, or areas of hyalinized necrosis which are suggestive of syphilis but also common in tuberculosis. There should, however, be no occasion to biopsy these lesions, if a reliable Wassermann report can be obtained.

Tuberculosis.—The usual clinical features of tuberculosis of the skeleton is that of a joint disease. Involvement of the spine, the hip, the knee and the ankle occurs in the order of frequency given. In the advanced case the clinical picture is typical. The deformity, the muscle spasm, the atrophy, the swollen joint, draining sinus, and the x-ray film indicating an essentially destructive process in the bones about the joint, are quite characteristic. But such outspoken pathology while presenting the optimum conditions for diagnosis affords the minimum of opportunities for treatment. The weight of progressive practice is therefore toward earlier diagnosis at a time when the nature of the disease process is more obscure and difficult to determine. Such early diagnosis is not only an urgent consideration, but the many conflicting claims for newer modes of therapy have increased the demands for accuracy in ascertaining the condition under treatment.[1]

Laboratory aids in the early diagnosis of joint tuberculosis which have met with a definite sphere of usefulness are threefold: serologic (including the tuberculin reaction), bacteriologic and pathologic.

Numerous modifications of the von Pirquet's tuberculin test have been proposed. The original test which was epidermal and employed two small drops of old tuberculin placed on the skin which was then scarified, has been variously estimated in accuracy. A negative test which is reliable in ruling out the disease may be in error where an overwhelming tuberculous infection or an acute complicating illness is present. When the reaction is positive as evidenced by a white papule with a red areola appearing in twenty-four to forty-eight hours the chances of error are greatest as the age increases beyond four years. The percentage of false positives is from 10 to 25 per cent. The Mantoux test[2] in which the needle introduces the tuberculin intradermally is more accurate than the Pirquet test and even higher accuracy can be obtained when both human and bovine tuberculin are used. Maxwell[3] believes that swelling in addition to the erythema which is maximum in forty-eight hours is necessary for a positive test. The injection should be controlled by using normal saline introduced in a similar manner at two points, one above and one below the site of the tuberculin inoculation. When these more accurate modifications are employed the reaction is

sufficiently valuable to be used as a routine in all suspected cases, but the results obtained must be considered as contributary evidence rather than conclusive from the angle of diagnosis.

For this reason various serologic tests have been proposed. Some of these have been planned on the basis of complement fixation in imitation of the Wassermann reaction while others are based upon a flocculation test planned after the manner of the Kahn test for syphilis. One of the more recent attempts which is being given a trial in Europe is the Vernes resorcine test.[4] The method employs the serum of the patient to which is added an equal amount of 1.25 per cent of resorcine reagent in aqueous solution. The test, however, has not proved specific and it can be stated in general that it and similar attempts do not compare in value with modifications of the von Pirquet method.

Bacteriologic confirmation of the disease is dependent upon the recovery of the organism from the affected joint. Unfortunately a smear of material and the demonstration of acid-fast bacilli by staining with the Ziehl-

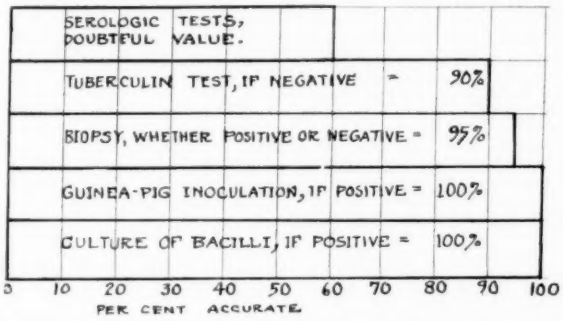
SEROLOGIC TESTS, DOUBTFUL VALUE.
TUBERCULIN TEST, IF NEGATIVE = 90%
BIOPSY, WHETHER POSITIVE OR NEGATIVE = 95%
GUINEA-PIG INOCULATION, IF POSITIVE = 100%
CULTURE OF BACILLI, IF POSITIVE = 100%
0 10 20 30 40 50 60 70 80 90 100
PER CENT ACCURATE

Fig. 5.—Chart showing the comparative accuracy of laboratory tests in the diagnosis of bone tuberculosis. The percentage of accuracy shown is an approximation of figures from various sources and attempts to represent a consensus of clinical opinion on the tests indicated.

Neilson carbolfuchsin method as employed for the sputum in phthisis cannot be applied here with any degree of success. Guinea pig inoculation can be resorted to although it has the disadvantage of requiring six weeks for a result and of being inconclusive when negative. Direct culture using the proper medium* has peculiar advantages in joint tuberculosis in that other organisms acting as secondary invaders are not present if there is no draining sinus. Culture is more rapid than guinea pig inoculation although it requires a more careful technic.[5]

Many surgeons with much experience in joint tuberculosis are turning to the exploratory operation as a conclusive diagnostic method in early cases. Where the tissue cannot be identified by its gross pathology the presence of tubercules can be demonstrated microscopically and in many instances acid-fast bacilli are found in sections stained with carbolfuchsin. So much hinges on establishing the correct diagnosis early, and good surgical technic is sufficiently safe, that the procedure is justifiable. Thus, whereas surgery

*Petroff's medium which contains egg white and other media which employ potato are suitable for this purpose.

in syphilis may be avoided and supplanted by the use of the Wassermann reaction and antisyphilitic treatment, in tuberculosis surgical exploration as a diagnostic procedure is superseding the tuberculin and serologic tests. (Fig. 5.)

It is well at this point to mention the possibilities of protecting children from tuberculosis infection of the bones and joints by vaccination with the Bacillus Calmette Guerin (B.C.G.). Calmette[6] and his coworkers recommend giving one centigram of the fresh culture of this organism by mouth to infants within the first ten days of life, the dose to be repeated twice at forty-eight hour intervals. Immunity develops in four weeks as evidenced by a positive tuberculin reaction. In France over 100,000 children have been treated by this method with a reduction in mortality from tuberculosis among children from 15.9 per cent to 3.4 per cent. While all of the claims set forth by these workers have not been confirmed, where infants are born of tuberculous parents this procedure warrants consideration. The material is supplied by the Pasteur Institute to public health agencies upon request.

Osteomyelitis.—While in chronic cases of osteomyelitis, the diagnosis usually rests jointly with the clinical picture and the roentgenogram, in acute osteomyelitis the need for early intervention makes it imperative to proceed before positive x-ray findings become manifest. In deciding upon the exploration, malaise, local point of tenderness, high fever, and a leucocytosis are helpful signs. A white blood cell count is of unquestionable importance in such early diagnosis although it must be borne in mind that in young patients with a rapidly growing sarcoma of bone a leucytosis of over 15,000 may be present as well as a temperature of over 100°.

The finding of pus at exploration is diagnostic but in its absence cultures of the material removed by the drill should be made since the recovery of pyogenic organisms in such instances is conclusive evidence of osteomyelitis. Since a bacteriemia is necessary to transport the organism from its portal of entry to its locus in the bone it is important to bear in mind the value not only of culturing the diseased area but also of taking blood cultures in cases of acute osteomyelitis.

Wilensky[7] has emphasized both the diagnostic and prognostic importance of this laboratory procedure in acute osteomyelitis. When positive blood cultures are obtained they are helpful in differential diagnosis and also in deciding on further treatment and estimating the outcome. While one to five colonies of bacteria per cubic centimeter do not count against a good prognosis, a larger or uncountable number of colonies (in the neighborhood of 100) indicates an overwhelming infection. The type of organism is also of some importance. The recovery of staphylococcus in the blood stream at the outset of the case when the x-ray is negative indicates the possibilities of bone involvement and favors surgical exploration. The presence of streptococcus in the blood stream Wilensky believes favors a more conservative attitude as far as exploration of the bone is concerned. Of course in many instances the blood culture will be negative regardless of the nature or progress of the infection. Nevertheless blood cultures should be taken in all suspected cases of osteomyelitis and repeated from time to time during the course of the disease.

When staphylococcus can be cultured in numbers or repeatedly from the blood stream, blood transfusion is a valuable asset in the treatment. If a hemolytic streptococcus septicemia exists the administration of an antiserum should be employed in addition to the transfusion. In these severe cases it is important to follow the white count closely from day to day and to use some form of nonspecific protein therapy when the number of leucocytes falls below 15,000.

The laboratory has added a valuable and novel asset to the treatment of late acute and chronic osteomyelitis in the form of the maggot therapy of Dr. William S. Baer.[8] In this treatment the larvae of the blue and green bottle flies are placed in the wound and sealed with a colloidin dressing and allowed to feed on the necrotic material in the wound and to destroy the infective bacteria present. The method is particularly valuable for chronic osteomyelitis. The availability of the maggots for this important new treatment is entirely dependent upon the laboratory. The flies must be maintained with the proper food and environment, the food including spoiled meats in which the eggs are laid. These eggs are then sterilized in a solution of 1-1000 biehloride of mercury plus 1 per cent hydrochloric acid and then transferred to sterile food composed of ground liver, where within eight to twenty-four hours they become maggots, ready to be placed in sterile containers and carried to the patient.

Mycotic Infections.—The resemblance of a mycotic infection of the bone to both tuberculosis and malignancy makes the diagnosis a difficult one in many instances, and yet it is extremely important that the correct interpretation of the patient's condition be arrived at early in order that the proper treatment may be instituted and prove of value in these difficult cases. Mycotic infections usually enter by way of the skin and finally arrive at the bone beneath either by direct extension or by metastasizing to some distant region. At the point where the bone is affected the osseous material is eaten away and the surrounding soft parts are indurated so that clinically the area frequently resembles a late stage of malignant tumor. Cultures made from an open sinus or by aspiration may be grown on Sabaraud's medium and within forty-eight hours a positive growth should be obtained which shows the typical mycelia or arrangement of the fungi involved. Smears are also helpful in the diagnosis and should not be omitted. The pus is often characteristic in infections due to actinomyces, containing typical grayish or yellowish granules.*

The majority of the fungus infections which involve bone belong to the group of mycelia properly referred to as actinomyces. (Fig. 6.) The usual actinomycotic infection involves the bones of the jaw or the foot and is conventionally recognized by its so-called sulphur granule. However, in many of the cases reported the lesions, if occurring clinically in the foot, have been loosely referred to as the madura foot, or if studied bacteriologically have often been classed as actinomycosis on the basis of granule formation. In reality three sets of organisms may be involved. One of these is

*To demonstrate actinomyces in tissue removed for biopsy, the material should be fixed in formalin or 95 per cent alcohol and stained by the Mallory method (*Mallory and Wright Pathological Technic.* W. B. Saunders Co., Philadelphia).

a group of maduromycoses which contains such species as scedosporia, asperigilla, etc. These contain definite thread-like hyphae which reproduce by spores. Second, the actinomyces which consist of thin branching mycelia, and third, an unrelated group which may produce a similar clinical picture

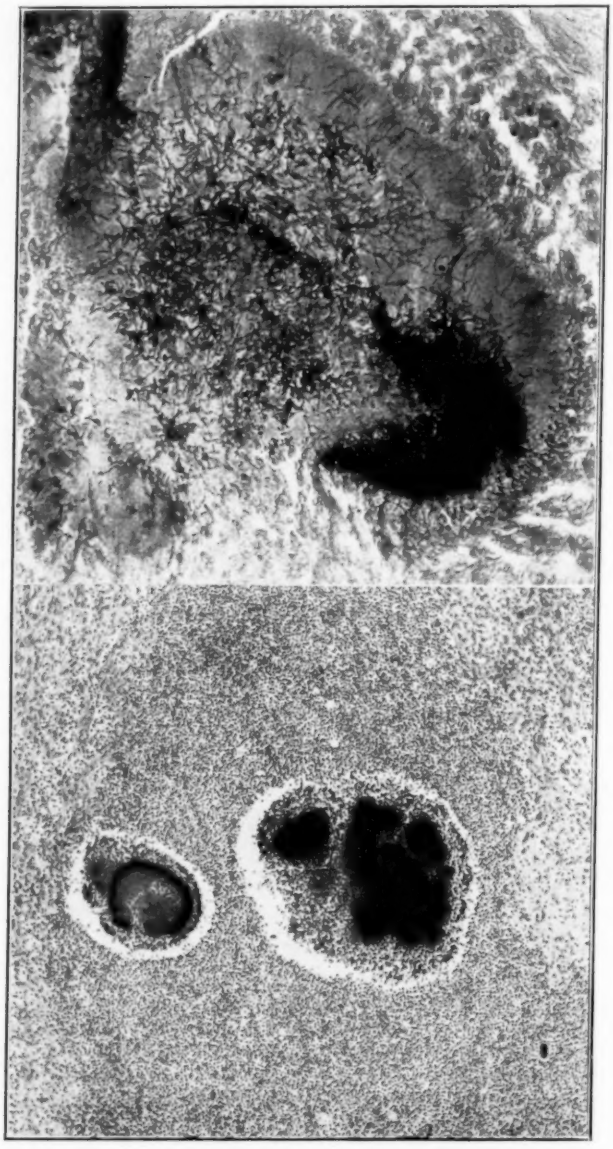

Fig. 6.—Microphotograph showing the characteristic granules and branched formation of mycelia found in the pus of a case of actinomicosis. (Mallory's stain for mycelium.)

the blastomycoses of a yeast type which grow by budding, forming large spheroidal cells surrounded by a refractive membrane.

Other true branching organisms with bulbous ends have been described[9, 10] in cases involving bone under the term of streptothrix without

the presence of sulphur granules, but these undoubtedly belong to the group of actinomyces referred to above. In all of these infections early diagnosis followed by prompt and adequate iodide therapy is essential to successful treatment.

In these conditions the regional lymph nodes are usually enlarged and it is important for the clinician to know that a biopsy on such glands is usually contraindicated. In the first place it is erroneous to believe that sarcoma, if present, will be found in these enlarged nodes for it is a safe rule that this type of malignancy never involves the glands. Metastatic carcinoma may be found but it is rare for the metastatic cancer to involve the distal portion of an extremity where these infections are often located and also to involve the bone in patients under thirty. If fungus infection is present, the removal of the glands may prove troublesome indeed, because the low-grade inflammation of the surrounding tissue and the danger of introducing a secondary infection.

Arthritis.—The most prevalent type of chronic infectious or rheumatoid arthritis is both a medical and surgical problem. In cases not too far advanced the dental surgeon and surgeon are often called upon to remove suspicious teeth, tonsils, to drain sinuses or investigate the prostate or gall bladder which are supposedly serving as foci of infection. In a small group of cases marked and immediate improvement follows the removal of these foci, but unfortunately in the majority of cases the results are not so encouraging.

The percentage of satisfactory results may be definitely increased by resorting to laboratory procedures. All cases in which the teeth or tonsils are removed or where the prostate is treated by massage should have a culture made of the suspicious focus. A vaccine then may easily be prepared and administered and a number of cases otherwise not benefited will show marked improvement. Such an attempt at vaccine therapy should be made in all refractory cases and when no other focus of infection is found an enlarged lymph node may be excised or punctured and the material cultured. Not infrequently the causative organism has been thus obtained and a successful vaccine prepared.

While it is true that attempts to isolate a single specific causative organism for chronic arthritis have failed and numerous vaccines prepared from favorite strains in many laboratories have fallen far below expectation, for routine treatment the preparation of the vaccine is so simple that it should be given a trial. Wherever possible a fresh autogenous vaccine should be made by sterilizing with 1 per cent phenol, the cultures obtained from a suspicious focus, rather than employing any stock preparation.

It is apparant from the more recent work in this field of rheumatoid conditions, that the bacteriologic approach to chronic arthritis has definite limitations, and the disease must be looked upon as involving general systemic factors such as the slowing down of the metabolism in the regions affected and a change in the circulation of the synovial membrane. However, dietetic régimes (other than the reduction of weight in patients suffering from obesity) and attempts at organic therapy have not met with

any degree of success to date. The most promising modes of treatment other than those aimed at the infection are measures which have as their object an increase in the blood supply to the joint region.

II. ROENTGENOLOGIC DIAGNOSIS

A good roentgenogram is indispensable to adequate diagnosis and as a guide in treatment in surgery of the bone and joints. Together with the microscopic section it furnishes the only reliable method of differentiating between benign and malignant neoplasms of the bone and should never be omitted in a thorough clinical study. To give in detail the roentgenologic features of the various diseases and tumors of the bone is obviously beyond the scope of this paper. However, it is highly important to set down in so far as possible to do so a few of the working rules for the use of the x-ray film particularly as applied to neoplasms of the bone.

Uses of the Roentgenogram.—An x-ray film of the bone should be made after every severe injury with pain on motion of the part or when there is increase in tenderness, swelling and pain over bone. The pictures should be retaken if not clear, and views should be obtained in two different directions and also of the opposite sides for comparison, for early changes are otherwise indiscernible.

Multiple foci of pathology or diffuse lesions in bone of uncertain nature in the first film taken demand a film of the entire pelvis (lumbar spine and upper femur included) and chest (with upper arms included) to rule out multiple bone or joint involvement which usually contraindicates surgery, and narrows the possibility for diagnosis.* In either single or multiple bone lesions, if acute osteomyelitis is ruled out the x-ray films may be used for consultation when in doubt before surgery. Surgery is indicated in very few of the multiple lesions and the minority of the single lesions. There is no harm in waiting for a confirming opinion and while doing so, the part should be put at rest.

The x-ray machine as well as radium therapy may be used as a diagnostic test when malignancy is suspected. If acute osteomyelitis is not present it is well to give deep x-ray therapy to determine whether or not the lesion is radio sensitive. A rapid decline in the size of the tumor after a few treatments indicates a Ewing's sarcoma or a very cellular metastatic growth.

Before operating for a malignant lesion of bone, an x-ray film of the chest should be made to rule out metastases. In interpreting such a film it is important to give the patient the benefit of the doubt and attribute most suspected pulmonary metastases to healed tuberculosis unless there is other corroborative evidence of metastases, such as cachexia, recurrent tumor, or fluid in the chest.

Benign Tumors.—It can be stated with a fair degree of probability that a lesion involving the bones on either side of a joint is benign as are multiple lesions producing gradual bowing of the bone, or found in children up to the age of twenty. The most common benign tumors follow:

Exostosis.—In the x-rays the typical exostosis forms an osseous out-

*In such multiple bone lesions the urine should be examined for Bence Jones bodies.

growth differentiated into cancellous and compact portions which merge imperceptibly with identical zones in the normal bone beneath; and has an overlying cartilaginous growth with varying degrees of calcification and an occasional superimposed bursa containing fluid or calcareous material. It is usually situated in a long bone in a patient between the ages of ten and twenty years. (Fig. 7-*A*.)

This group of tumors may occur in multiple form, associated with a congenital disease of the skeleton in which shortening and bending of the bones is one of the most frequent of the numerous skeletal deformities. This multiple form of the disease is hereditary and is known as hereditary deform-

Fig. 7-*A*, *B*, *C*, *D*.—X-ray features of benign bone tumors.

Fig. 7-*A*.—Shows the roentgenogram of a typical exostosis. A pedicle of normal bone continuous with the shaft of the femur supports a proliferative cartilaginous cap. These lesions are typically benign and need no treatment unless causing pain or manifesting a sudden growth.

ing chondrodysplasia. Both the single and multiple forms of exostoses are benign lesions. The single forms can be cured by excision and the multiple form is helped by corrective operations after the growth period. Secondary chondrosarcoma may arise in either single or multiple exostoses.

Benign Chondroma.—A central bone destructive lesion in the small bones of the hands or feet or centrally located in the sternum is usually a benign chondroma (Fig. 7-*B*). These tumors expand the cortex, occasionally perforate it, and produce a central translucent area.

Bone Cysts.—The benign bone cyst occurs in the shaft of the long bones in children and produces a central rarefied area which expands the cortex symmetrically and leads to pathologic fracture in 50 per cent of cases (Fig. 7-*C*). This tumor usually occurs in the shaft near the metaphysis, of the upper humerus, upper femur or upper tibia. The cavity in the bone may be traversed by lines of trabeculation and tends to ossify after fracture or after

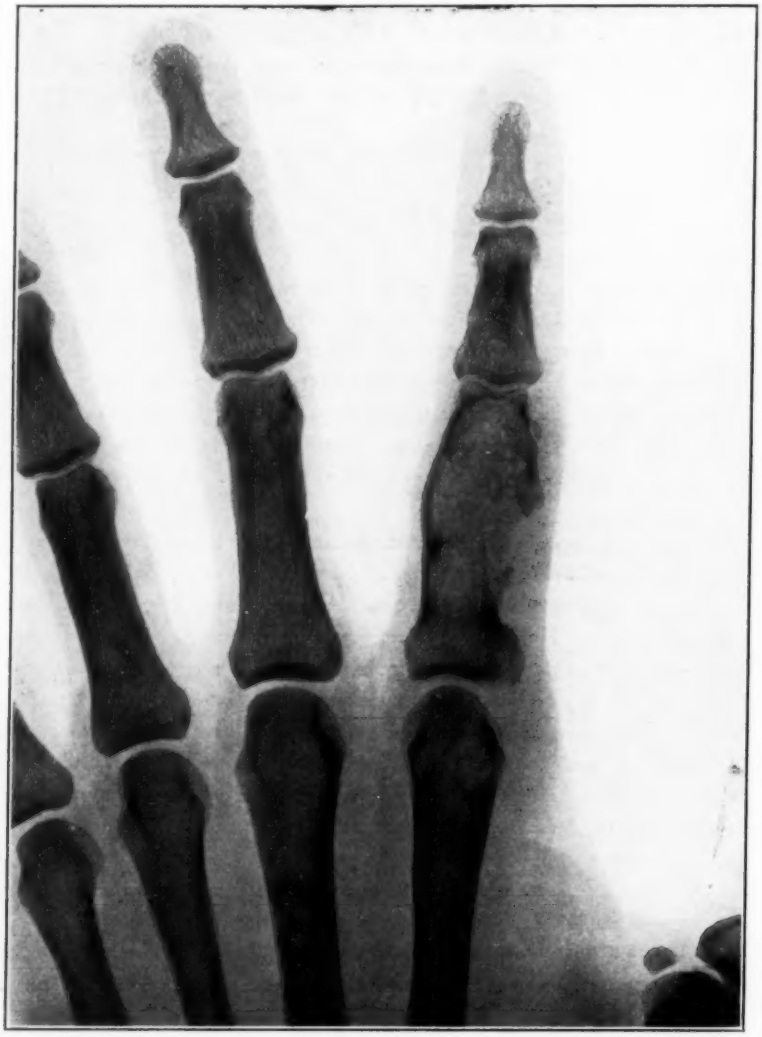

Fig. 7-*B*.—Shows the roentgenogram of a typical benign central chondroma in the proximal phalanx of the forefinger. These lesions may be cured by simple curetting followed by cauterization with 50 per cent zinc chloride when occurring in the small bones of the hand or foot. When occupying a central location in a large bone, the prognosis is more serious and they should either be left alone or treated more radically.

a crushing operation. Arrestment of the lesion without obliteration of the cavity results in the latent bone cyst. Progression of the lesion when the presence of the cyst is complicated by other skeletal diseases such as Paget's Osteitis Deformans, Fragilitas Ossium, Osteomalacia, etc., leads to a generalized fibrocystic disease of the skeleton.

Benign Giant Cell Tumor.—A benign giant cell tumor usually occurs in the epiphysis of an adult, destroys the bone and expands the cortex asymmetrically and often perforates the bone shell extending into the soft parts (Fig. 7-*D*). This lesion is most frequent in the lower femur, upper tibia, and lower radius and gives a more acute clinical picture than does the bone cyst. The usual sequence of events is trauma, pain, tumor and pathologic fracture. The lesion is progressive unless surgical intervention occurs or x-ray therapy is administered.

Malignant Tumors of the Bone.—Most of the malignant tumors of the bone occur in children or young adults as single lesions known as osteogenic sar-

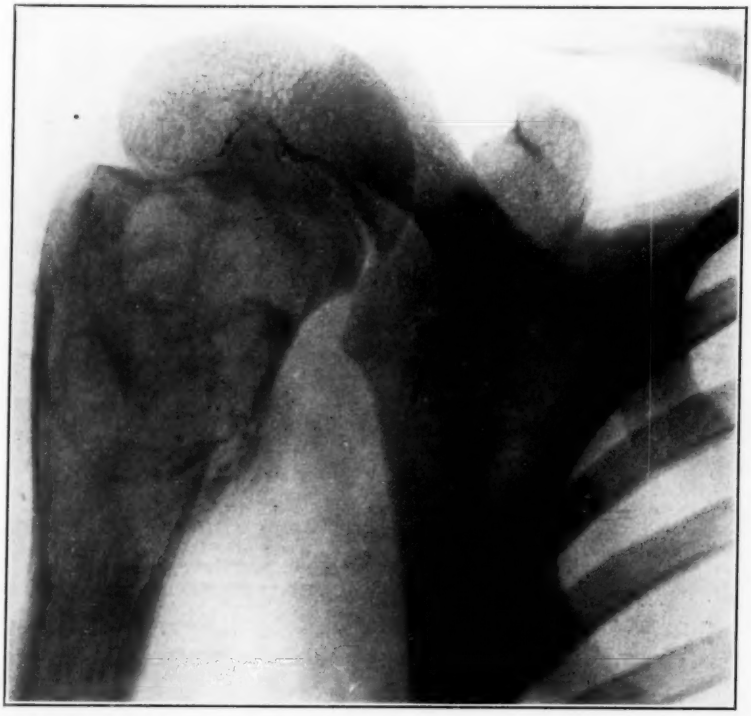

Fig. 7-*C.*—A typical benign bone cyst in the upper end of the humerus showing a pathologic fracture. Such a lesion may be treated as a simple fracture with good results. Operation is not essential.

coma. Metastatic carcinoma and multiple myeloma constitute most of the malignant neoplasms observed in patients over thirty-five years of age.

Osteogenic Sarcoma.—The most prevalent types of this sarcoma are periosteal growths producing right angle new bone formation and causing sclerosis or osteoporosis in the shaft of the bone beneath. An occasional form of osteogenic sarcoma may arise within the cancellous bone and be predominantly bone destructive. (Fig. 8-*A* and *B.*)

The osteoblastic or sclerosing form which is one of the prevalent types is characterized in the x-ray film by dense radiating new bone in the periosteal zone in the metaphysis of the long bones of youthful patients, and is most universally recognized as the "sun ray" type of sarcoma of bone. This form

of tumor is most frequent between the ages of fifteen and twenty-five years, in the lower femur and in the upper tibia. It runs a fairly acute course, initiated by trauma and accompanied by pain, tumor and dysfunction. The average duration of symptoms is under ten months. In the tumor new bone proceeding from the subperiosteal region of the metaphysis raises the periosteum on the outward side and infiltrates and scleroses the marrow cavity inwardly. An osteogenic sarcoma composed of cartilage accompanied by ossification and cystic degeneration may occur. In the x-ray it is faintly

Fig. 7-*D*.—Roentgenogram of a benign giant cell tumor in the lower end of the radius. These benign lesions may be cured by curettement followed by chemical or thermal cauterization. They show a definite tendency to recur. Deep x-ray therapy has been used successfully but takes much longer to effect a cure and does not offer the benefits of biopsy.

visible as a subperiosteal shadow with an infiltrating outward margin which may be emphasized by a few sparse spicules of calcified or ossified material. It does not involve the cortex or medullary cavity until late in the disease when it invades these areas and bone destruction is the result.

Ewing's Sarcoma.—Ewing's sarcoma widens and scleroses the shaft of the bone in young adults producing an onion peel-like periosteal reaction. Late in the disease there is a definite soft part shadow and osteolysis in the marrow cavity (Fig. 8-*C*). The lesions may metastasize late in the disease to other bones. The disease never primarily involves an epiphysis. It shows

the usual malignant symptoms for bone of pain and tumor, followed by dysfunction, and may give the systemic reactions of fever and leucocytosis.

Metastatic Carcinoma.—Metastatic carcinoma produces either a multiple or single area of medullary bone destruction in adults (Fig. 8-*D*). The source of the tumor varies, but the most frequent sites of the primary growth are a cancer of the prostate, a cancer of the breast, a hypernephroma, carcinoma of the thyroid, or somewhere in the female genitalia or gastrointestinal tract. Solitary areas of metastatic carcinoma to bone occur most frequently in the upper end of the humerus or femur, and are extremely rare below the knee or elbow. They may also involve the trunk or the skull. The central

Fig. 8-*A*.

Fig. 8-*B*.

Fig. 8-*A*, *B*, *C*, *D*.—Roentgenologic features of malignant bone tumors

Fig. 8-*A*.—A typical sclerosing osteogenic sarcoma showing right angle new bone formation and sclerosing of the marrow cavity. Approximately one-third of the cases showing this type of x-ray picture may be cured by early amputation.

Fig. 8-*B*.—Roentgenogram showing the typical rapid bone destruction caused by an osteolytic variety of osteogenic sarcoma. The soft part shadow and the location distal to the knee joint as well as the age of the patient which is under thirty favors a diagnosis of sarcoma rather than metastatic carcinoma. This patient was cured by an early amputation. Cures in this group represent about 15 per cent of the total.

area of bone destruction in the x-ray, rapidly enlarges and destroys the cortex from within, outwardly, with little bone expansion. Multiple areas of skeletal involvement by metastatic tumors may also be osteolytic in character and central in location. Such lesions have a tendency to involve the pelvis and the spine in addition to the upper ends of the humerus and

Fig. 8-*C*.—An early case of Ewing's sarcoma of the tibia. Note the expansion and sclerosis of the shaft and the onion peel formation in the periosteum. This tumor is radiosensitive and this type of treatment with and without radical surgery has resulted in 12 per cent of five year cures.

Fig. 8-*D*.—Roentgenogram of metastatic carcinoma involving the pelvis, femurs and lumbar spine. Note the mottled areas of bone destruction and bone formation. The disease is practically always fatal, but deep x-ray therapy is very useful in alleviating pain and prolonging life.

femur. They are prone to produce pathologic fracture and bending of the bone and in the x-ray are visible as confluent and mottled areas of bone destruction in medullary locations. Osteoplastic involvement of the bones by skeletal metastases is most frequently a diffuse affair and in addition to the absorption of bone always present, there is in the subperiosteal region a laying down of irregular new bone of moderate density.

III. PATHOLOGIC DIAGNOSIS AND BIOPSY

Uses of Biopsy.—It can now be stated with a fair degree of assurance that a biopsy on a bone lesion, properly performed and followed within a few days by the appropriate treatment, is a safe procedure in lesions of the

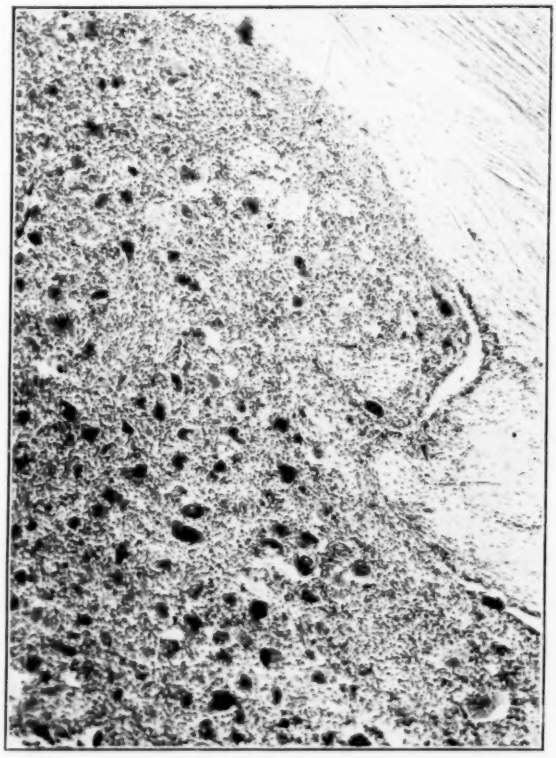

Fig. 9-*A*, *B*.—Comparison of benign and malignant giant cell areas.

Fig. 9-*A*.—Shows a typical benign giant cell tumor. There are many large multinucleated giant cells imbedded in a uniform stroma of small round and spindle cells.

bone. There is one type of tumor of the bone which is either malignant or potentially malignant that is an exception to this rule, and this is the chondroma or chondrosarcoma occurring in a long bone or in a bone of the skeletal trunk. These cartilaginous tumors of the large bones contain pockets of tissue of a fluid or a semifluid myxomatous nature, and if this material is spilled in the wound, it has a decided tendency to give rise to secondary transplants. If such a growth is suspected from the roentgenogram, it is best not to explore unless an immediate amputation is contemplated. Biopsy

under such conditions necessitates an immediate frozen section and indeed it is wisest in amputating for any bone tumor to employ frozen section rather than to make a separate operation of the exploratory procedure. This brings up the question of a rapid and accurate frozen section technic and the feasibility of sectioning material from bone without awaiting decalcification.

At Dr. Bloodgood's clinic it has been the practice for years to make such a rapid preparation for microscopic examination at all operations upon the bone. In all the more cellular tumors it is always possible to secure a bit of tissue relatively free of bone and then selecting an old knife reserved for

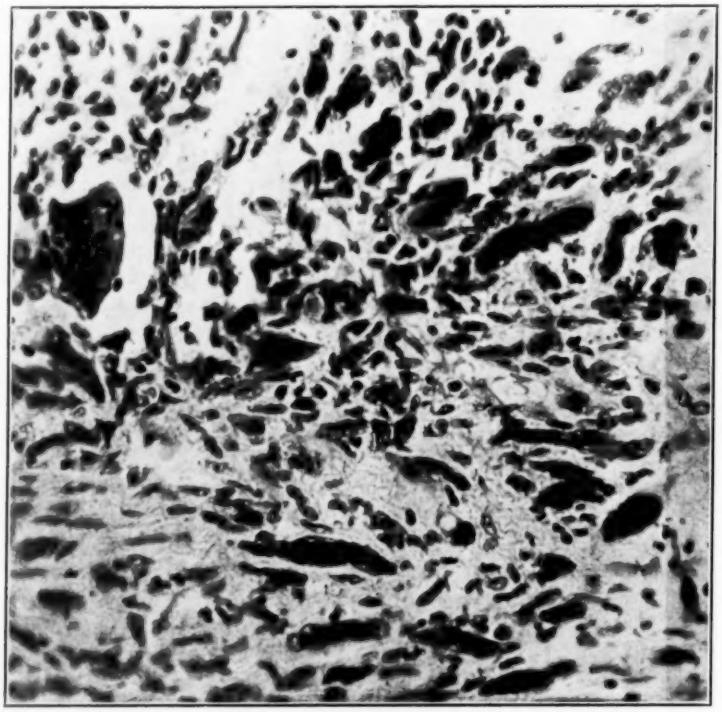

Fig. 9-*B*.—Photomicrograph showing the margin of a giant cell area occurring in osteogenic sarcoma. In the upper left hand corner is seen a giant cell imbedded in a small round cell stroma but below are the large malignant fibroblasts typifying sarcoma.

this purpose, to cut frozen sections on the freezing microtome regardless of any small bits of calcified material that might be encountered. If callus about an inflammatory area is to be examined or the margin of sclerosing periosteal tumor, a strip of the periosteum is always selected, to which there will be sufficient material clinging for diagnosis. It is also helpful to secure a section from a soft part immediately overlying the tumor which will often show invasion by the tumor cells. The more familiar the surgeon operating is with the frozen section technic and the interpretation of such sections, the better equipped he is to secure suitable material for biopsy.

In the interpretation of a frozen section much depends upon the staining method and the practice with the procedure as a routine. In this clinic

a mixture of azure and Erie garnet* is used for rapid staining and the tissue which is immediately washed in water and mounted in glucose is examined under a strong artificial light.

The following rules are helpful in determining when to employ biopsy in a suspected neoplasm of the bone. Biopsy should be performed before treating by a deep x-ray therapy a suspected giant cell tumor which has perforated the cortical bone. This procedure should also be carried out before amputating an extremity for any bone lesion. All operations in which curetting is contemplated should have an immediate frozen section upon entering the tumor area.

Fig. 10-*A*, *B*.—Comparison of benign and malignant new bone formation.

Fig. 10-*A*.—Shows the formation of regular spicules of new bone imbedded in fibrous tissue at the margin of the inflammatory area. A regular layer of osteoblasts is applied to the spicules. This is typical of benign new bone formation.

Biopsy may be omitted when a lesion of bone is clinically inoperable and when x-ray therapy is used palliatively. It also may be omitted in a tumor which is malignant in the roentgenogram and which shrinks rapidly under irradiation. This procedure need not be resorted to in experienced hands when a resection of the bone is performed for a tumor diagnosed malignant by the x-rays in a patient with a negative Wassermann reaction.

Interpretation of the Microscopic Section.—In the interpretation of the section secured at the biopsy there are certain well-defined problems of pathologic diagnosis with which the surgeon should be familiar. As a clinician he may not be expert in rendering the final decision but he should recognize the typical case and know when his pathologist is on problematic

*Procurable from the Abbott Laboratories, North Chicago, under the name of Azure number 136.

ground. The problem of pathologic diagnosis in bone tumors may be discussed under four separate heads:

1. Interpretation of giant cell areas
2. Differentiation between benign and malignant new bone
3. Differentiation between benign and malignant spindle cell proliferation
4. Differentiation of various round cell tumors

Fig. 10-*B*.—Shows a malignant proliferation of osteoblasts enclosing an irregular and diffuse matrix of osteoid substance. This is typical of sclerosing sarcoma and gives a characteristic appearance in the x-ray. See Fig. 8-*A*.

Giant Cell Areas: The typical giant cell tumor is benign and is characterized by many large multinucleated cells embedded in a stroma of small round or spindle cells. When the giant cells are small or sparse, and when the stroma contains large spindle cells with big vesicular nuclei malignancy is to be suspected the case is usually one of osteogenic sarcoma. (Fig. 9-*A* and *B*.)

Benign and Malignant New Bone: Benign reactive new bone formation occurs in inflammation and at the margin of bone cysts. It is characterized

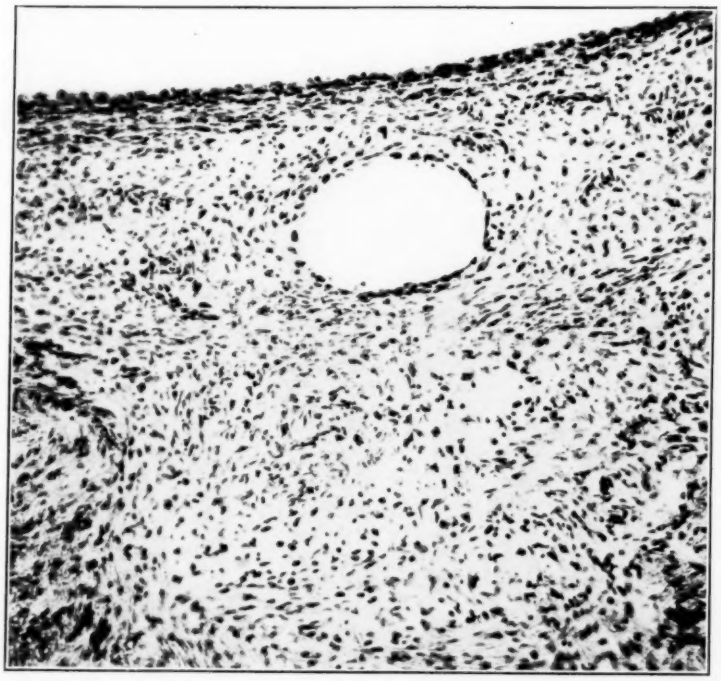

Fig 11-*A*, *B*, *C*.—Comparison of benign and malignant fibrospindle cell areas.

Fig. 11-*A*.—Microphotograph taken from the margin of a benign bone cyst. Note the edematous fibrous tissue in which the cells containing small nuclei are separated by a large amount of intercellular substance.

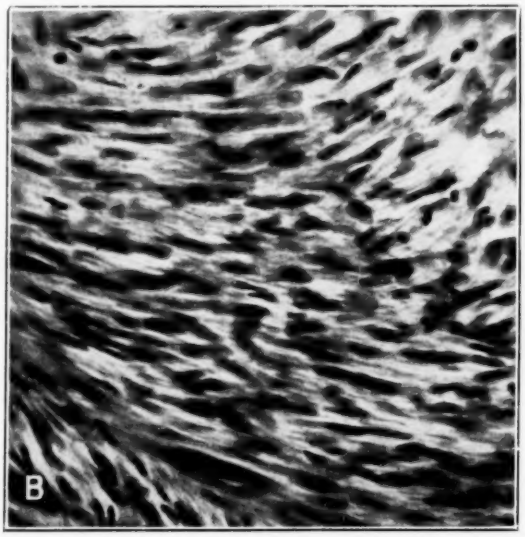

Fig. 11-*B*.—Shows the typical microscopic appearance of a fibrospindle cell sarcoma. The nuclei are larger, contain many mitotic figures and the cells are closely packed.

by the formation of definite bone spicules, the spicules being surrounded by an orderly single row of osteoblasts. In osteogenic sarcoma there is a sclerosing form in which new bone predominates. This malignant new bone has a diffuse osteoid matrix and an irregular proliferation of bone spicules, the osteoblasts present are scattered everywhere in great numbers bearing no fixed relation to the osteoid substance (Fig. 10-*A* and *B*).

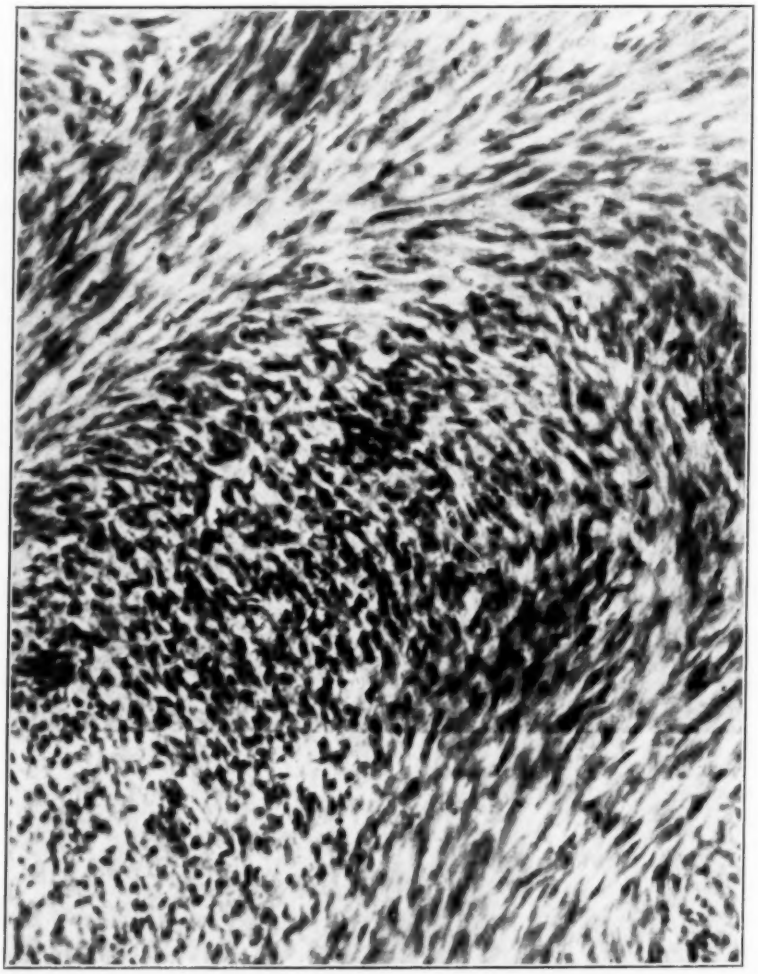

Fig. 11-*C*.—Shows a small spindle cell or oat cell type sarcoma. Here the nuclei again are tightly packed and give the appearance of round cells when cut at right angles. The diagnosis of malignancy is based upon the extreme cellularity of the growth and pleomorphic changes in the nuclei.

Benign and Malignant Spindle Cell Proliferation: Benign spindle cell proliferation occurs at the margin of benign giant cell tumors, in the wall of bone cysts and in periosteal fibromas overlying the bone. The spindle cells show a definite tendency to produce fibrils and strands of collagenous material. Their nuclei are always small and rarely multiple. Malignant spindle cell proliferation is found in osteogenic sarcoma and in periosteal fibro-

sarcoma. Here the spindle cells may be very large with big nuclei containing many mitotic figures and often taking on a binucleated form. The intercellular substance is sparse. Occasionally a small spindle cell sarcoma is found in the periosteum. In such cases the nuclei predominate, the cells are tightly packed and there is no intercellular substance. (Fig. 11-*A*, *B*, and *C*.)

Differentiation of Round Cell Tumors: This is the hardest microscopic problem for those nonexpert in pathologic diagnosis. Osteomyelitis and specific infections of the bone generally show more variation in the type of cells present than do the malignant round cell tumors. In osteomyelitis in addition to the lymphocytes, polymorphonuclears and plasma cells are present. In syphilis and tuberculosis the lymphocytes tend to form into definite tubercles or gummas and giant cells may be present.

The malignant round cell tumors include Ewing's sarcoma, multiple myeloma and the cellular metastatic carcinomas. In Ewing's sarcoma the cells are uniform in size, have very little cytoplasm, contain many mitotic figures and are separated at intervals by coarse fibrous trabeculae. In multiple myeloma the cells have a definite cytoplasm with an eccentric nucleous containing chromatin arranged in a spoke-like manner and large multinucleated forms may be present. In cellular carcinoma the cells also have a definite rim of cytoplasm; but the nuclei are centrally placed, are larger and the cells tend to take an alveolar formation. (Fig. 12-*A*, *B*, *C*, and *D*.)

IV. STUDIES OF THE BLOOD CHEMISTRY

Rickets was the first disease of bone in which chemical studies on the calcium and phosphorus content of the blood serum found practical application. It has been definitely shown that animals develop rickets on a high calcium and low phosphorus diet provided vitamin D and ultraviolet light are not administered to counteract the disturbance. In children suspected of this disease, if the blood serum calcium and phosphorus stated in milligrams per 100 c.c. yield a product below 30, it may be stated with assurance that active rickets is present, whereas if the product is over 40, healing or no rickets is present.* In addition to this diagnostic test for rickets, laboratory studies have shown the value of vitamin D (found in sterols) and ultraviolet light in the prevention or cure of the disease.

Calcium and phosphorus studies (Hunter[11]) on the blood have been applied more recently to analyze the group of diseases generally referred to under the heading of osteitis fibrosa. It has been found that when the blood calcium is normal or elevated and the blood phosphorus is low and in addition the excretion of calcium in the urine is much increased in a patient who is suffering with multiple bone cysts, that a parathyroid tumor is usually present. This syndrome is now recognized as distinct from a single bone cyst in which the calcium and phosphorus values are normal. For the first time, therefore these laboratory studies have made it possible to separate hyperparathyroidism with associated von Recklinghausen's disease from such diseases as bone cysts, Paget's osteitis deformans, and osteomalacia.

*The normal values in the blood serum are 4 to 6 mg. per 100 c.c. for phosphorus and 9 to 10 mg. per 100 c.c. for calcium.

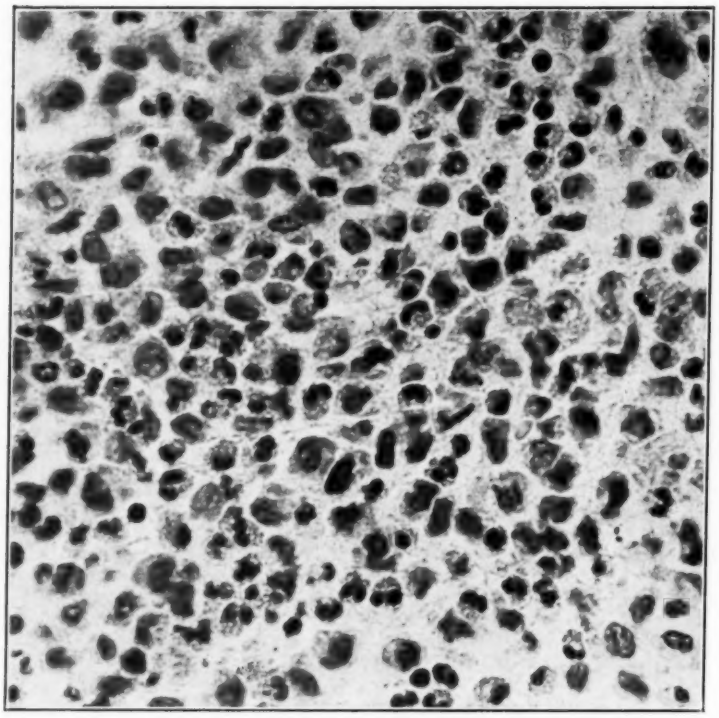

Fig. 12-*A, B, C, D.*—Differential microscopic diagnosis of round cell tumors.

Fig. 12-*A.*—Photomicrograph made from tissue removed in a case of osteomyelitis. The type of cells vary widely with the polymorph, the plasma cell and the lymphocyte predominating.

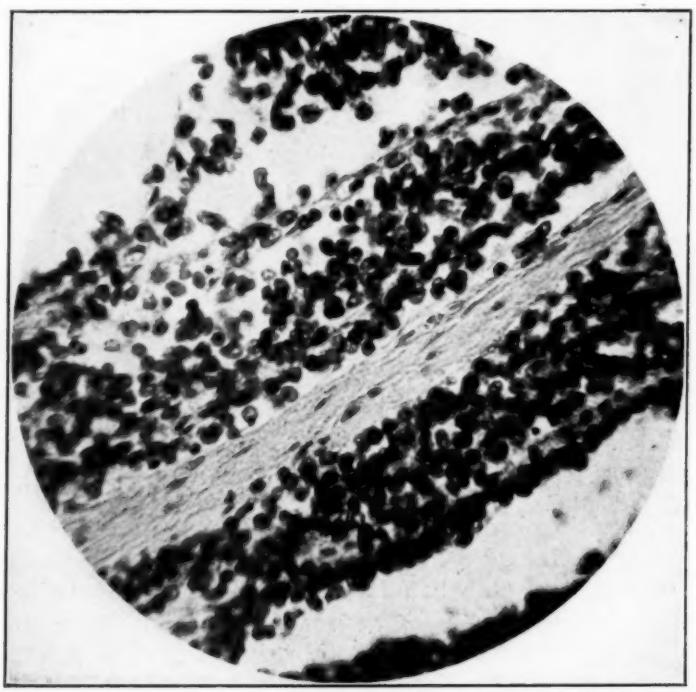

Fig. 12-*B.*—A photomicrograph of a Ewing's sarcoma showing the uniformity of the round cells present, the density of their nuclei and the scarcity of their cytoplasm. The fibrous strand traversing the tumor area is typical.

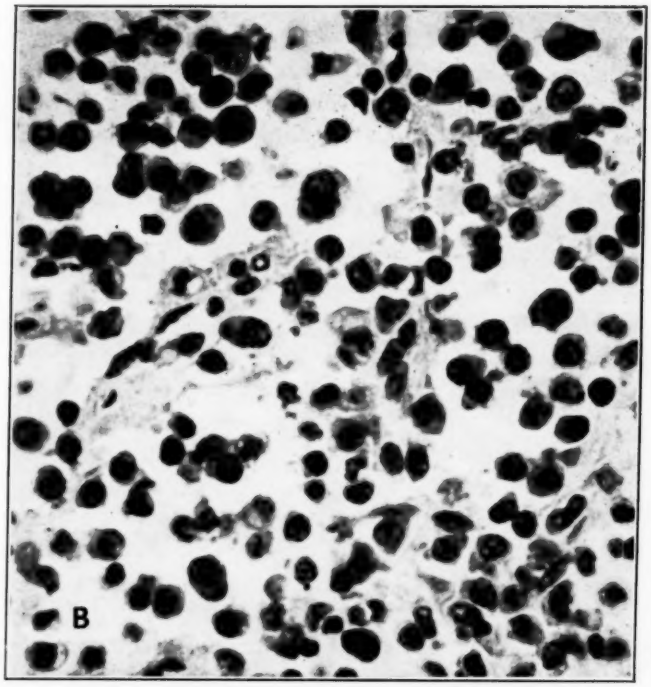

Fig. 12-*C*.—A photomicrograph of a typical plasma cell multiple myeloma. Note the definite cytoplasm, the assymmetrical nuclei and the spoke-like arrangement of chromatin within the nuclei.

Fig. 12-*D*.—Photomicrograph of a metastic carcinoma of breast occurring in bone. The cells tend to be arranged in small acini and each cell has a definite amount of cytoplasm. The bone spicules shown are undergoing necrosis.

In 1924 Peterson claimed on the basis of experimental studies that a product of calcium and phosphorus in the blood serum below 30 made for nonunion in fractures and that disturbance in the values of these inorganic constituents of the blood was largely responsible for most of the clinical cases of nonunion fractures. Since that time the general opinion has swung away from this emphasis upon the importance of blood calcium and phosphorus in the healing of bone (Speed[12]). It can, however, be safely stated that these chemical studies together with an analysis of the relationships between internal secretions and inorganic metabolism has done much to enlighten many dark and obscure corners in bone and joint pathology, and offer a most promising field for fruitful investigation.

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THE ALLEGED TOXIN OF BURNED SKIN*

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FOR years the assumption has been prevalent that death from a superficial burn is due to a toxin from the burned skin circulating in the blood. The literature on the subject is filled with assertions and denials of nearly every aspect of the problem and one gains the conception that the whole matter is in a most chaotic state. If the evidence for a toxin is carefully sifted it becomes quite apparent that some elusive and indefinable agent is the cause of death. However, whether this agent is a chemical substance or a set of conditions induced by a burn has not been decisively answered. From the standpoint of specific substances the most diverse compounds have been suggested and in turn each has been discarded. Less attention has been paid to the possibility that the burn may induce within the organism a set of conditions incompatible with life.

From a perusal of the literature[1] one gains the impression that the mere diversity of suggested poisonous compounds is to be accepted as an expression of stages in the progress of chemical knowledge concerning proteins and their disintegration products. Each period of chemical advance has had its suggested toxin. For example, there have been periods when proteoses and peptones were assumed to be responsible for the detrimental or even fatal effects of a burn, as well as of various other pathologic conditions. In like manner, "ptomaines," pyridine-like bodies, guanidine salts, toxic proteins, nucleoproteins, etc., have been designated. At present it is to histamine that one is inclined to ascribe active participation.

The latest and apparently most convincing attempt to explain the toxemia of burns is that of Robertson and Boyd[2] in which it is claimed that there is formed in the burned skin a toxin, "which circulates in the blood, either in or adsorbed by, the red blood corpuscles, and which causes symptoms seen in bad superficial burns, and in some cases death." "The toxic substance consists of two portions, one of which is thermostabile, diffusible, and neurotoxic; the other is thermolabile, colloidal and necrotoxic. Chemically the toxin consists of primary and secondary proteoses."

EXPERIMENTAL

For a number of years we have been engaged in investigations relative to the effects of burns; and the statement by Robertson and Boyd of noteworthy toxic symptoms, after injection of extracts of burned skin has impelled us to subject this type of investigation to further scrutiny. In no previous report have such consistent detrimental effects of burns been detailed. We have endeavored to follow as exactly as possible the technic developed by Robertson and Boyd except that the burn was produced by an electric flat

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iron instead of by the application of hot iron plates. Inasmuch as the manner of preparation of the extracts is of prime importance in our interpretation of the effects of skin extracts the method of Robertson and Boyd is quoted verbatim. "Pieces of burned skin, 280 to 300 square centimeters in size, were used. The skin was freed from subcutaneous tissue and fat and washed free from blood. It was then finely ground with sea sand in a meat chopper. This was well covered with freshly distilled water or normal saline, and allowed to stand twelve hours. It was placed in a canvas bag and the fluid squeezed out in a press. Four volumes of absolute alcohol were added to the fluid obtained. This was filtered. The extract was concentrated, and the alcohol removed by evaporation in a vacuum, at a temperature not exceeding 40° C. A clear yellowish slightly viscid fluid was thus obtained. This was filtered through a Berkfeld filter, and then used for inoculation. Extracts of normal skin prepared in the same way were used for controls.

"Ten cubic centimeter doses of extract of normal skin were injected intravenously in four pigs (guinea) of 250, 280, 260 and 263 grams respectively. No ill effects whatever followed these injections. Similar negative results were obtained following the injection of normal skin burned postmortem.

"The injection of extracts of burned skin from animals or children resulted in the development of the symptom complex of burn toxemia. Doses of 1 to 2 cubic centimeters, representing roughly $\frac{1}{60}$ to $\frac{1}{30}$ of the total extract obtained from pieces of skin 280 to 300 square centimeters in size, were sufficient to cause these symptoms in twenty pigs of 275 to 300 grams in weight. Eight of the twenty died in general convulsions. Necropsy findings were the same as those seen in superficial burns."

The Influence of Skin Extracts on Guinea Pigs.—The protocols of Robertson and Boyd reveal that extracts made from skin immediately or several hours after a burn show marked toxic effects when injected intraperitoneally into guinea pigs. We have made extracts of skin at different intervals after a burn and typical illustrative protocols of our own experience follow.

Approximately 280 square centimeters of burned skin from the abdomen after a three-hour burn were ground with sand, covered with 120 c.c. of physiologic saline and allowed to stand twelve hours. After twelve hours 480 c.c. of absolute alcohol were added to the filtrate and the process completed according to Robertson and Boyd, outlined above. A normal rabbit was anesthetized and the skin similarly treated. The final burned skin extract was equal to 66 c.c.; that of the normal skin, to 35 c.c.

TABLE I

PIG	WEIGHT	DOSE OF EXTRACT	REMARKS
	GM.	C.C.	
5	320	7	Within 5 minutes all animals except 6 and 9 became drowsy and
6	330	7	fell over on their backs. The eyes rolled downward. Occasional
7	315	7	twitching of the legs occurred. They all appeared on the point of
8	350	7	death. Pigs 6 and 9 developed symptoms more slowly. Within an
9	340	6	hour all seemed somewhat better. Pig 7 was found dead 8 hours
10	380	5	later. Autopsy revealed about 10 c.c. of peritoneal fluid and pul-
11	305	4	monary congestion. The remaining animals eventually recovered.

Experiment With Extract of Burned Skin.—Seven pigs were injected intraperitoneally with varying quantities of the extract. (Table I.)

TABLE II

PIG	WEIGHT GM.	DOSE OF EXTRACT C.C.	REMARKS
1	250	6	These animals behaved in exactly the same way as did those receiving extract of burned skin. Pig 1 was found dead within 20 hours. Pulmonary congestion was in evidence on autopsy.
2	301	6	
3	362	6	
4	420	6	

Experiment With Extract of Normal Skin.—Four pigs were injected intraperitoneally with normal skin extract. (Table II.)

These experiments demonstrate that the extracts of *both* burned skin and normal skin contain a substance, or substances, inducing marked but identical symptoms when injected into guinea pigs. Repetition of the experiments gave a variety of results. In some instances the extract obtained from burned skin was toxic; that from normal skin was without influence. Again the reverse situation was presented. In other experiments neither extract was toxic.

At first it was thought that possibly the variation in potency of the extract was due to the presence or absence of barium sulphide which was employed as a depilatory. Experiments in which barium sulphide was omitted and in which hair was removed by clipping yielded variations in every way comparable to those previously obtained. It is therefore evident that barium sulphide is not the effective agent.

If the toxic material present in the skin extracts is of a protein nature or is a protein degradation product the temperature at which the extraction is allowed to proceed for a period of twelve hours may play a significant rôle in the quantity of toxic substance present since the extent of proteolysis is so directly dependent upon the temperature. Accordingly extracts were made of both burned skin and normal skin in which the extraction took place in a refrigerator at 10° C. as opposed to one at a temperature of 37° C. The potency of the extracts was just as variable and uncertain at one temperature as at the other. It may therefore be concluded that the degree of proteolysis of the skin protein is without influence.

Robertson and Boyd state that "boiling the extract for two minutes before injecting altered the effect produced. Nervous symptoms of the same character ensued but the animals (seven in number) all recovered." They have further stated that the toxic substance is nonvolatile. We have prepared active extracts of both burned skin and normal skin and find with Robertson and Boyd that on boiling they rapidly lose their toxic effect. If such extracts are evaporated to dryness on the water-bath and the residue is dissolved in a volume of water equivalent to the original volume of fluid evaporated, such solutions injected in suitable doses fail to elicit any symptoms in guinea pigs. This experiment therefore demonstrates that the loss of toxicity of these potent extracts is due either to the effect of heat upon the active agent or that the effective substance is volatile. To determine which of these hypotheses is correct an active extract was boiled for one-half

hour under a reflex condenser. The injection of this solution demonstrated that it had lost none of its potency. From this experiment one is forced to the conclusion that heat in itself is not effective in diminishing the toxicity of the extract. Moreover since the potency of the extract is lost on evaporation of the solution on the water-bath it is quite evident that the loss of toxicity is due to volatilization of the effective agent—a conclusion in direct opposition to that of Robertson and Boyd. If an active extract is subjected to distillation on a sand-bath it may be demonstrated that the distillate on injection into guinea pigs produces the typical effects of the original extract and that the residue is without influence. If an extract inducing a typical reaction in the guinea pig is subjected to redistillation under diminished pressure below a temperature of 40° C., the distillate will show the typical reaction and the residue is inert.

From all these considerations we have come to the conclusion that the effective substance in our skin extracts is alcohol. The presence of alcohol explains quite satisfactorily the toxicity of normal skin extracts as well as those from burned skin, and it also accounts for the variation and inconstancy of toxic effects observed by us for different extracts. An effective extract was subjected to analysis and found to contain 9.8 per cent alcohol (by volume). Our own experiments differ from those reported by Robertson and Boyd in that their extracts of normal skin never induced any toxic symptoms.

Having accepted the hypothesis that alcohol is the effective agent in our skin extracts, it was of interest to determine the effects of different concentrations of alcohol when injected intraperitoneally in the guinea pig. In this connection it was also desirable to discover the strength of alcohol which can be detected by the sense of smell. In all of our skin extracts the presence of alcohol would never have been suspected from the odor present.

The Influence of Different Strengths of Alcohol Upon the Guinea Pig.—The symptoms obtained with alcohol were identical with those characteristic of our skin extracts and these results lend support to our hypothesis that the presence of alcohol in the skin extracts is the effective agent in producing toxic symptoms and even death.

From the work of Robertson and Boyd it is very difficult to estimate to what degree alcohol was removed from their extracts. Certainly the sense of smell would allow the presence of a marked alcohol concentration. They merely state that the alcohol was removed by evaporation in a vacuum at a temperature not exceeding 40° C. Under such conditions, unless the solution is taken to dryness, some alcohol will always be present since both alcohol and water will distill off, the alcohol not leaving the mixture with much greater rapidity than the water. In our own investigation the total volume of the water-alcohol solution approximated 600 c.c.; the final filtrate from the Berkefeld filter varying from 15 to 80 c.c. Robertson and Boyd state that "doses of 1 to 2 cubic centimeters, representing roughly $\frac{1}{60}$ to $\frac{1}{50}$ of the total extract obtained from pieces of skin 280 to 300 square centimeters in size, were sufficient to cause these symptoms in twenty pigs of 275 to 300 grams in weight." From these figures it is quite evident that the total extract obtained by Robertson and Boyd varied between 50 and 120 c.c., figures which compare favorably

TABLE III

PIG	BODY WEIGHT GM.	ALCOHOL INJECTED C.C.	ODOR	REMARKS
			2 Per Cent	
1	400	2	Negative	No influence
2	370	4	Negative	No influence
3	305	6	Negative	No influence
4	380	8	Negative	No influence
			4 Per Cent	
5	410	4	Negative	No influence
6	415	6	Negative	No influence
7	430	8	Negative	No influence
8	490	10	Negative	No influence
			10 Per Cent	
9	260	5	Faint	No influence
10	410	10	Faint	Marked typical effect in 10 minutes
11	410	10	Faint	Marked typical effect in 10 minutes
			15 Per Cent	
12	520	10	Positive	Reaction in 3 minutes. Very severe. Several convulsions. Appears normal in 4 hours. At the eighth hour found dead. Much fluid in peritoneum and many small hemorrhages in gastrointestinal tract.

with some of our own. If this assumption is correct then it can be positively stated that the extracts employed by Robertson and Boyd contained relatively high percentages of alcohol. Indeed the quantity of alcohol present was sufficient to account for the symptoms observed.

As a further support for our hypothesis, the following experiment may be cited:

A mixture of 80 c.c. of physiologic salt solution and 320 c.c. of absolute alcohol was subjected to distillation under diminished pressure at a temperature below 40° C. until only 70 c.c. remained.

Ten c.c. of this solution were injected intraperitoneally into a guinea pig (Pig 1) of 525 gm. body weight. Within five minutes the pig presented the symptoms typical of skin extracts. The remaining 60 c.c. of the fluid was returned to the distillation apparatus and reduced to a volume of 40 c.c. of fluid.

Ten c.c. of this solution were injected as before into a pig (Pig 2) of 490 gm. body weight. There was a most severe reaction in a period of three minutes. Again the fluid remaining was subjected to distillation until a volume of 14 c.c. remained.

Ten c.c. of this solution were injected into a guinea pig (Pig 3) of 470 gm. body weight. In five minutes symptoms were in evidence which however were not severe and which lasted for a short period only.

On the following day Pig 1 was found dead with many hemorrhages of the gastrointestinal tract.

Pig 2 was comatose and subject to convulsions.

Pig 3 appeared normal.

The next day Pig 2 was found dead with hemorrhages of the gastrointestinal tract.

Pig 3 was normal and remained so.

It is quite apparent that at certain stages the residual volume of this saline-alcohol mixture is quite capable of inducing all the symptoms (and even death) characteristic of the skin extracts.

It is our conviction therefore that when skin extracts prepared in the manner described by Robertson and Boyd cause toxic symptoms the effective agent is alcohol rather than a toxin from the burned area.

There yet remains the discrepancy between the results of Robertson and Boyd and our own with respect to the toxicity of normal skin extracts. There is no indication in their paper as to how many normal skin extracts were employed. It is quite possible to miss the toxic action by variation in the extent of distillation to which we ascribe our own varied results. In our experiments each time an animal was burned a normal control animal was used, it being subjected to the same period of anesthesia as the burned animal and it was killed at the same time. In this way a large number of normal extracts were prepared. In our preliminary experiments had reliance been placed upon the results of one or two extracts of normal skin, it is quite probable that we also might have missed the apparent toxic action of such extracts.

Does Blood From Burned Animals Produce Toxic Symptoms When Injected Into Guinea Pigs?—Having indicated that burned skin elaborates a toxic substance Robertson and Boyd carried their investigation a step further and as a result asserted that "doses of 2 or 3 cubic centimeters of whole blood (citrated) from rabbits or children suffering from burn toxemia injected into pigs resulted in the onset of toxic symptoms consisting of alternate periods of drowsiness and excitability, weakness of the hind legs, convulsions, and in five cases, death. Autopsy findings in the fatal cases were identical with those seen in burned animals." On the other hand, doses up to 15 c.c. of whole blood induced no symptoms. From these statements it would appear that the burn toxin had been absorbed and produced its detrimental influence by way of the circulation.

We have been sufficiently interested in this problem to carry through a number of experiments on the toxicity of the blood of rabbits with superficial burns, in comparison with results obtained with the blood of normal rabbits. Like Robertson and Boyd we have used the guinea pig as the test animal. The blood of the burned animals was drawn at different intervals after burning. In certain instances coagulation was prevented by addition of citrate. In other experiments the blood was defibrinated. For details see Table IV.

An inspection of these results will demonstrate that the degree of toxicity after the intraperitoneal injection into the guinea pig of blood from the burned rabbit is little different from that obtained when normal blood is similarly introduced. It must therefore be concluded that these experiments present no evidence that the blood of a burned animal contains a "burn toxin."

Our experience with burns leads us to doubt the existence of a "burn toxin," and to believe that the persistence of this viewpoint is an obstruction

in the way of clarification of the burn problem. We are of the opinion that a burn establishes a set of conditions in the organism which will account for all the symptoms attributable to a toxin. This set of conditions is initiated by a great loss of fluid from the blood to the wounded area resulting in a marked concentration of the blood and subsequently to an inefficient circulation eventually leading to tissue asphyxiation and death. We have discussed elsewhere[3] the probable production of anatomic changes (hemorrhages, ul-

TABLE IV

THE INFLUENCE OF INTRAVENOUS INJECTION OF RABBITS' BLOOD UPON THE GUINEA PIG

PIG	BODY WEIGHT GM.	BLOOD INJECTED C.C.	REMARKS
		A. Blood of Normal Rabbits	
		Citrated	
1	350	4	Immediate jumpy reaction; weakness of hind legs; drowsiness.
2	325	4	No reaction. Dead next day. Autopsy showed pneumonia and hemorrhages of small intestine.
3	370	4	Immediate jumpy reaction; weakness of hind legs; drowsiness.
		Defibrinated	
4	335	6	No reaction.
5	250	6	No reaction.
6	625	10	No reaction.
7	405	5	No reaction.
8	600	7	No reaction. Found dead on second day after injection. Autopsy showed peritonitis and hemorrhages of intestines.
		B. Blood of Burned Rabbits	
		Citrated	
9	250	3	No immediate reaction. Dead in 6 hours. Autopsy showed intestinal hemorrhages.
10	255	5	Immediate jumpy reaction for a few minutes. Dead in 6 hours. Hemorrhages in intestine.
11	340	4	As with Pig 10. Dead on second day after injection. Autopsy showed peritonitis and hemorrhages.
12	380	4	No reaction.
		Defibrinated	
13	560	10	No reaction.
14	420	4	No reaction.
15	415	6	No reaction.
16	370	4	No reaction. Found dead on third day after injection. Autopsy showed hemorrhagic peritonitis.

cers, etc.) sometimes observed in burned cases. These likewise may be attributed to a single fundamental cause, namely, a local change in the circulation induced by heat penetration to the organs.

The opinion has become established that there are three phases of systemic effects after a burn which lead to death, 1. shock, productive of early death; 2. a toxin from the burned area inducing death within a few days, and 3. secondary infection causing death at later intervals. Shock certainly occurs, but since animals burned under anesthesia never exhibit shock symptoms unless some part of the central nervous system has been subjected to the heat, it follows that the symptoms of shock are not related to the production of a toxin at the site of the wound.

For the second phase we believe that it is unnecessary to postulate a toxin. Instead we would substitute the existence of a degree of blood con-

centration incompatible with the maintenance of physiologic rhythm. Certain it is that if in this phase the level of blood concentration can be held within certain well-established limits death does not occur.[4] In this phase it appears most improbable even theoretically that a toxin plays a rôle. We have shown elsewhere[5] that this is the period when absorption from the burned area proceeds with extreme slowness and we doubt the probability that any substance heretofore suggested as a burn toxin is capable of absorption from the burned area in sufficient concentration to cause death. We do not exclude histamine, which as Harris[6] has shown probably occurs preformed in the skin and is merely released by a heat injury. If strychnine[3] in lethal doses will not elicit symptoms when injected into the burned area, it is quite unlikely that other compounds of equal or lower toxicity will do so.

In the third phase it is quite probable that death is to be ascribed to secondary infection.

Assuming that these viewpoints are correct, then in the treatment of burns attention should be directed to the prevention or alleviation of shock, to the maintenance of blood concentration of a degree compatible with life, and to local treatment of the wound to prevent infection and to facilitate healing. From our conception of the problem, the establishment of physiologic concentrations of the blood will do much to banish the present attitude of hopelessness of treatment of the systemic effects of a burn. Likewise the need for the assumption of a burn toxin will disappear.

CONCLUSIONS

The statement of Robertson and Boyd that burned skin contains a toxin was not corroborated. The symptoms obtained by these investigators after intraperitoneal injection into guinea pigs of extracts of burned skin are explained by the inclusion of significant quantities of alcohol in the extracts.

The blood of burned animals injected into guinea pigs exhibited symptoms and effects differing little from those obtained after similar injections of normal blood.

It is suggested that the postulation of a "burn toxin" is unnecessary since the symptoms and effects of a burn may be adequately explained by the establishment of blood concentration to a degree incompatible with life.

The large loss of fluid from the blood to the wounded area leads to the establishment of blood concentration. The relation of these viewpoints to the treatment of burns is discussed.

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A SIMPLE METHOD OF MAKING MICROPHOTOGRAPHS

By L. O. Dutton, M.S., Memphis, Tenn.

THE usefulness of microphotographs for purposes of readily available records and illustrations has been largely counterbalanced by the expense as well as by the necessity of expert assistance in the preparation of the photographs.

Fig. 1.*—Low power views of E. typhi colonies.

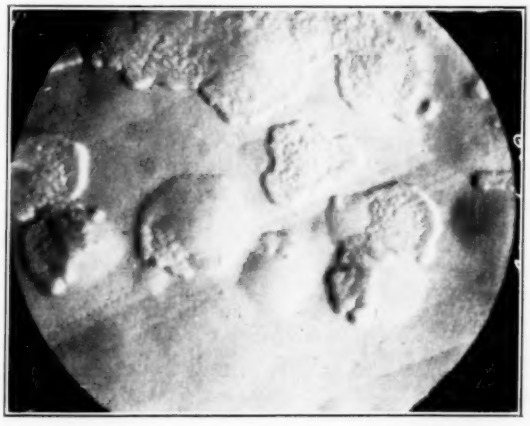

Fig. 2.—Low power views of E. typhi colonies.

Until recently moreover there has been no apparatus available that permitted the photographing of a field in the course of a routine examination. Some of the more modern cameras on the market overcome these objections but are still expensive.

*Figs. 1 and 2 illustrate the sterio effect obtained with oblique illumination.

Desiring to photograph some bacterial cultures during the course of some experiments several years ago I tried to use a cheap box kodak containing the simple so-called universal focus lens. This box had no modification of shutter or stops and was used with the lens in place. The instrument used was the No. 2 Film Pack Hawk Eye, made by the Eastman Kodak Co. No other apparatus than the camera, such as clamps, supports or light-tight connections are needed. The results obtained were so unexpectedly good that I have continued to use the method for several years and have successfully photographed a wide variety of subjects.

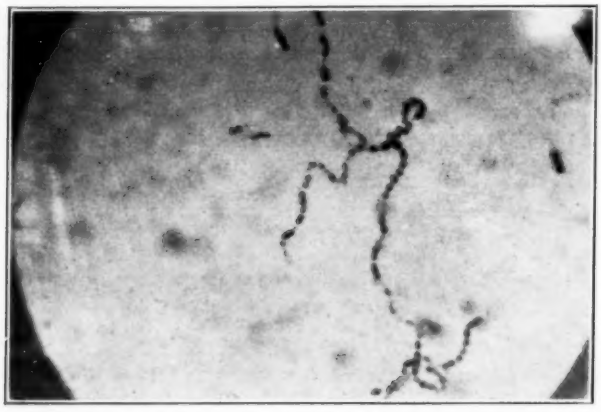

Fig. 3.—Oil immersion view of a gram stained streptococcus.

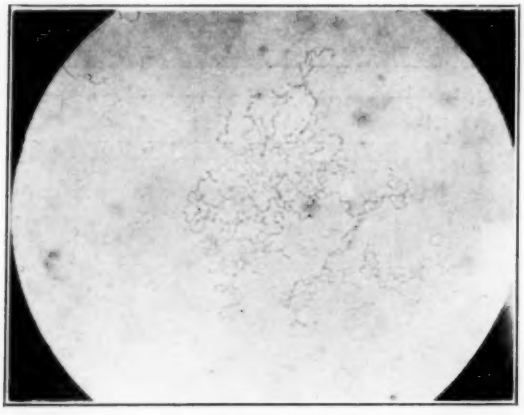

Fig. 4.—Low power view of young streptococcus growing on the surface of an agar plate. (Twenty-four hours.)

The procedure is extremely simple. When a suitable field is found the illumination is adjusted to secure the maximum visual detail without cutting the intensity too much. The box is then placed over the eyepiece so that the shutter and eyepiece are in line. There is no necessity for supports as the box readily balances in the proper position. As a rule for most types of box cameras and eyepieces there is no need for any special precautions in regard to light-tight connections. If trial shows that there is some light filtration around the

connection a small ring of velvet or other thick cloth pasted to the camera and surrounding the shutter will make a sufficiently light-tight connection with the rim of the eyepiece. The stop is set for time exposures and when the camera is in place the shutter is snapped. A small amount of unavoidable movement incident to this does not mar the results as the time consumed is so short in comparison to the total time of the exposure that it is negligible. At the completion of the exposure the shutter is again snapped, care being taken that what

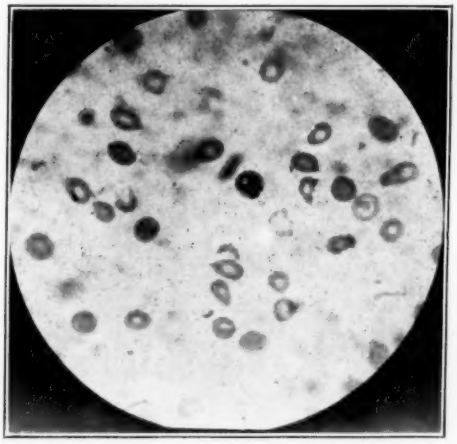

Fig. 5.—Oil immersion of a blood slide.

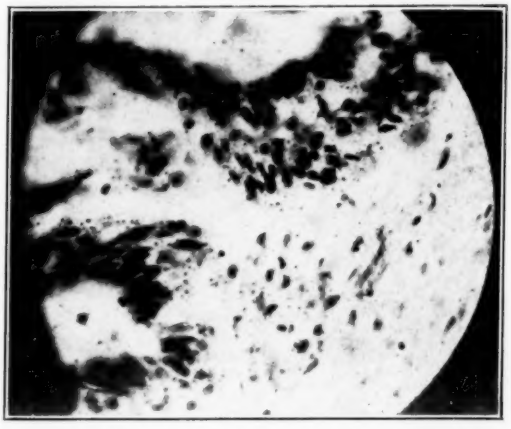

Fig. 6.—High power view of a hematoxlyn-eosin stained tissue. (Color filter and panchromatic films.)

movement occurs does not lift the box so that an accidental daylight exposure is superimposed upon the image. Ordinary building vibrations do not seem to blur the images. The camera being balanced upon the microscope what vibration occurs is simultaneous and thus of no consequence.

The time of the exposure will of course have to be determined by each operator for the existing conditions, depending upon the subject, strength of illumination, and magnification. As a rule exposures of from twenty seconds to two minutes have covered the range satisfactorily.

When using a monocular microscope it is necessary to be sure that the adjustment is tight enough to prevent the weight of the camera from displacing the tube. When using a binocular microscope it is only necessary to place the box over one eyepiece and to focus through the other. This can readily be done when the eyepieces are drawn as far apart as possible. The use of the binocular scope is especially useful when photographing fresh preparations where slight movement is likely to occur. The monocular tube on the other hand gives a better illumination for high power work.

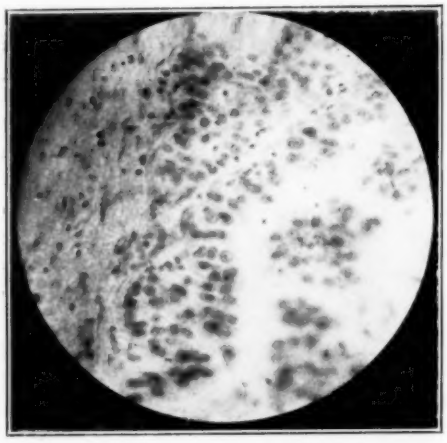

Fig. 7.—High power view of a hematoxlyn-eosin stained tissue. (Ordinary film with color filter.)

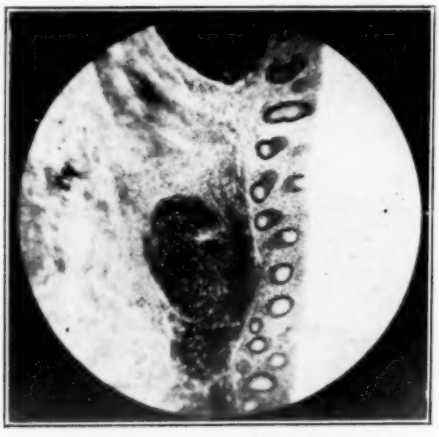

Fig. 8.—Low power view of a hematoxlyn-eosin stained tissue. (Ordinary film without filter.)

As a source of light I have used routinely a 75 watt frosted bulb. The more expensive special laboratory lights would in all probability serve better.

I have used this method on a wide variety of subjects, covering almost the whole range of common preparations. Tissue preparations give good results although it is of course necessary to use suitable filters to secure the maximum contrast. Panchromatic films are of great aid in securing good reproductions of stained tissues or other stained objects. (Panchromatic film packs of the

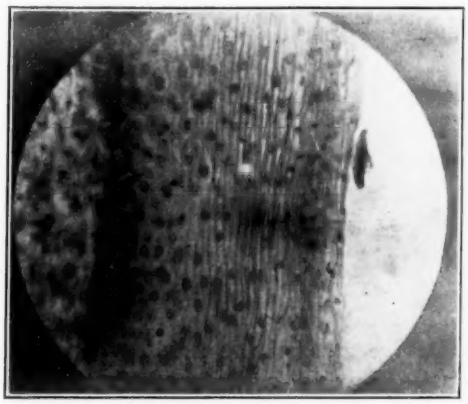

Fig. 9.—High power view of a hematoxlyn-eosin stained tissue. (Panchromatic film without filter.)

Fig. 10.—High power view of vitally stained Blastocystic hominis in fresh mounts.

Fig. 11.—High power view of ova of Oxyuris vermicularis in fresh mounts.

size used in the usual small box, 2¼ × 3¼ inches, can be obtained from the Imperial Dry Plate Co., Ltd., Cricklewood, London, N. W. 2.) Bacterial smears, colonies, fresh preparations of various kinds and even oil immersion views of living, unstained bacteria upon the surface of an agar plate have been successfully photographed.

In the study of bacterial colonies in particular, it is desirable to secure a stereopticon effect. This is readily done by the use of diaphragm below the condenser. Using low magnification the illumination is cut to a small pencil of light and then decentered until the desired effect is secured. In the absence of a movable diaphragm in this position the same effect may be secured after a little trial with a disc of cardboard perforated by a single opening of small size.

The advantages of the method are small expense, ability to photograph random fields during the course of routine examinations without disturbing the preparation, a minimum number of operations required, and the dispensing with focusing hoods or other dark-room methods during the operation.

One disadvantage is that with the size mentioned above it is sometimes impossible to secure a reproduction of the entire microscopic field. This is not a practical difficulty however as the entire field is desired only infrequently. The method is most useful when it is desired to secure a photographic record of many specimens or of many stages in the development of a single specimen, as for instance the growth of a bacterial colony.

The photographs (Figs. 1 to 11) were all made as described.

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A SIMPLE APPARATUS FOR CONTROLLING TEMPERATURE OF FLUID DURING INJECTION*

By M. A. Perlstein, M.D., Chicago, Ill.

IN EXPERIMENTAL, as well as in clinical work, where injections of fluid into the body must be made, it is necessary to keep the solution at body temperature. This is especially true in the case of intravenous and intrathecal injections particularly when large amounts of fluids are used, as in perfusion or lavage.

When the rate of flow is slow, the solution loses considerable heat by radiation. In its journey from the reservoir through the rubber tubing to the trocar or needle at the point of injection, the temperature of the fluid might

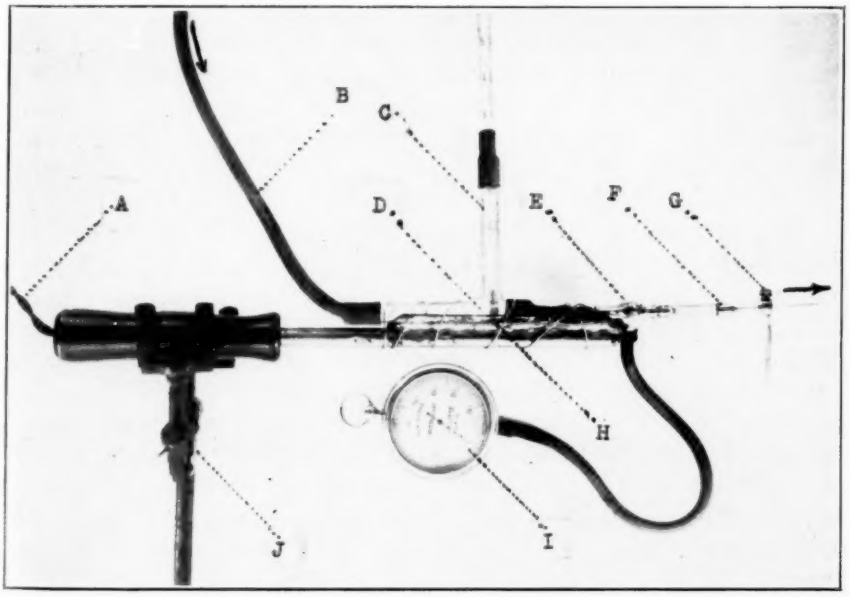

Fig. 1.—Heating Apparatus. (*A*) Cord of curling iron leading to rheostatic arrangement. (*B*) Rubber tubing from solution reservoir. (*C*) Vertical arm of T-tube containing thermometer. (*D*) Horizontal arm of T-tube, the right half of which is cut short. (*E*) Two-way stopcock to allow simultaneous reading of pressure. (*F*) Shoulder of cistern puncture needle, into which glass window is inserted. (*G*) Guard and retainer. (*H*) Curling rod with trough portion of clip soldered on. (*I*) Claude tambour manometer. (*J*) Clamp.

drop 20 to 25° C. The desirability of heating the fluid to the proper temperature as close as possible to its point of entrance into the body is thus evident.

The use of a heated metal jacket through which the solution passes just proximal to the point of injection with an automatic thermostatic control is

*From the Albert Kuppenheimer Fund of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research, Chicago.

probably the best means of attaining this end, but such a device is too expensive and not necessary for most work. The following device is inexpensive, practical, and is sufficiently efficient for most purposes. It can be constructed for about two or three dollars.

The heating element is the rod of an inexpensive curling iron (cost is $0.75 to $1.00). The half sleeve or trough portion of the instrument is separated from the clip, and its convex side is then soldered to the heating rod (Fig. 1 *H*). In order to govern the amount of heat produced in the curling iron rod, it is connected in series with a rheostat. A 40-watt lamp in a "Dim-a-lite" socket, an ordinary device for dimming an electric light in 3 or 4 steps (cost is $0.75 to $1.00), may be used as a rheostat, the bulb acting as a pilot light to indicate roughly the amount of current passing through. In this manner the heat produced in the heating rod can be regulated in four steps from zero to about one-half its full capacity of heat if there were no rheostat in the circuit. If it is desired to generate more heat in the iron (which for our work was undesirable), a "Dim-a-lite" capable of carrying the current for a 60- or 100-watt lamp may be used. The rheostat, together with a plug-in for the curling iron cord may be fastened to a wall board for convenience. If desired, a switch and fuse may also be inserted in the circuit.

The fluid to be injected is allowed to flow through a T-tube *(D)* which is placed as close as possible to the site of injection. The distal half of the horizontal arm is cut off as close as practicable to the vertical arm so that the thermometer placed in the vertical arm *(C)* will be as close as possible to the point of injection. The horizontal arm of the T-tube is fitted into the trough of the curling iron where it is secured by several turns of copper wire. If the solution flows slowly through the T-tube so that it is longer in contact with the heating rod, less heat will be needed in the curling iron than if the flow is rapid. By watching the thermometer and by turning the Dim-a-lite rheostat up or down, the temperature can be regulated fairly accurately within a few degrees.

We employed this device in cistern-lumbar lavage of the subarachnoid space with satisfactory results. Fig. 1 shows a cistern puncture needle *(F)* with a guard *(G)*, a glass window, and a two-way stopcock *(E)* to which a pressure manometer *(I)* is attached, so that both the temperature and pressure of injection can be observed simultaneously, during the course of the injection. The apparatus can be conveniently supported on a stand by means of a clamp *(J)* attached to the handle of the curling iron.

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EDITORIALS

The First International Congress for Microbiology

ON APRIL 28, 1927, at the occasion of the International Conference on Hydrophobia a preliminary meeting was held at the Pasteur Institute, Paris, for the purpose of founding an International Society for Microbiology. It was the unanimous conviction of those present that such an organization should be established.

The First International Congress for Microbiology was held at the Pasteur Institute, Paris, July 20-25, 1930, under the patronage of President Doumergue with Professor J. Bordet, president. At this Congress the International Society was founded.

The object of this Society is not only to encourage scientific production through creating a closer relationship between those who are working for it in the different countries, but above all, to create the unanimous opinion among its members that science should unite all nations in a common ideal of peace and lasting friendship.

The Society interests itself not only with bacteriology, but with all the sciences pertaining to Microbiology. The officers of the Society are a president, a general secretary and associate secretaries. These officers together with an International Committee constitute the governing body. The mem-

bers in each country form a National Section and elect the members to represent them on the International Committee. To become a member of the Society a candidate is recommended by the National Committee to the International Committee, which group elects all members as well as the officers for the Society.

A pre-Congress registration indicated an attendance of less than 500, however, on the opening day approximately 1,000 from over 27 different countries were present for the inaugural meeting. This unexpected attendance overtaxed the facilities of the Institute but every attempt was made by the Staff to care for the needs of all, which task was made all the more difficult because of language differences. From the initial meeting during which the delegates were welcomed by Professor A. Calmette (Professor Roux, director of the Institute was ill at the time) and responses were made by representatives of the various nations, to the final meeting held at Garches where the Institute farms are located, over 300 reports, communications and demonstrations were presented in the five official languages of the Congress on some topic pertinent to the subjects previously selected for consideration. The reports were grouped in three sections: Section I consisted of material related to microbic variability, scarlet fever, filterable viruses, undulant fever, cholera and influenza; Section II, lipoids in immunity, tissue culture and blood grouping; Section III, the decomposition of vegetable matter in the soil, immunity in plants, spirochetes in water, spirochetes in the blood and Bartonella infections. The reports were in the nature of reviews, the speakers emphasizing the more recent developments in their own special fields. At the conclusion of each paper a limited amount of time was devoted to the clarification of points which foreign languages had usually made somewhat obscure as well as to pertinent discussions. At the same time a great number of scientific exhibits held forth in every available space; conspicuous among these because of technical perfection were the moving pictures of microbic activity, bacterial dissection and tissue proliferation. For the evening the opera provided excellent entertainment; the general secretary's reception on Thursday evening; the general banquet on Friday, motor bus trips and private tours were provided for the intervening periods, if any. The meetings of the commission on taxonomy were marked primarily by the demonstration of confidence in the work of various individuals throughout the world in their attempts to solve the problem and by special interests in the spirit of cooperation of the Botanical Congress along the same line. Special arrangements were provided for the entertainment of the ladies including among other attractions visits to the monuments of Paris with special guides, a morning at the famous Goblens tapestry factory and finally an afternoon at one of the most fashionable dressmaking establishments in Paris. The appreciation of all of those who attended the Congress was tendered to the Local Committee on arrangements which had contributed so fully of its time and its efforts to build the success of the meeting which was rendered all the more arduous because of five official languages.

The Second International Congress will be held in Berlin in 1933.

—*M. H. S.*

The Virus of Psittacosis

THAT psittacosis is a disease due to a filterable virus which cannot be cultivated by ordinary bacteriologic methods is now generally recognized and amply confirmed by the reports of numerous investigators.[1]

Bedson and Western[2] recently report upon a study of some of the strains of virus which they isolated from an extended series of cases, both human and avian.

In 26 human cases a filterable virus was found in 15, six gave doubtful findings, and no evidence of a filterable virus could be found in five cases.

These workers were able to confirm the reports of others that white mice were susceptible to the psittacosis virus and can be utilized for its demonstration in human material. They were successful in two instances following the injection of 1 c.c. of citrated blood (0.5 c.c. injected intravenously and 0.5 intraperitoneally). The incubation period as already reported by Gordon, is apt to be prolonged (fifteen to twenty days).

Bedson and Western isolated the virus in 8 of 9 parrots and also demonstrated its presence in a canary and a Java sparrow, the birds all coming from an aviary in which an outbreak of psittacosis had occurred which was the source of human infection.

The authors also report upon the susceptibility of the guinea pig. The inoculation of a shaved area produces, after twenty-four hours, a raised slightly red papule the size of which is in proportion to the amount of virus used.

By forty-eight hours the lesion is larger, redder, and may show central necrosis. Vesicles are not formed, the necrotic area becoming a dry black scab.

Intratesticular inoculation is a satisfactory method for the demonstration of the virus.

Filtration and centrifugation experiments suggest that the virus particles are relatively large or else that the virus is absorbed to tissue particles of relatively large size.

While somewhat noncommittal as to the relation to the virus of the small cocco-bacillary bodies which have been described by various workers and which Lillie[3] has suggested be called Rickettsia psittaci, Bedson and Western have never failed to find them in infected mice although their presence in material of avian and human origin was inconstant. It was their impression that, in the mouse spleen, the number of bodies found was in proportion to the virulence of the virus.

The most satisfactory method for the preservation of the virus (up to two months) was by freezing the spleen.

Experiments concerning the therapeutic value of convalescent serum were not very encouraging, its neutralizing power appearing to be very low.

Experiments in mice indicated that psittacosis virus rendered noninfective by formalin (0.1 per cent concentration) was still capable of immunizing.

The various strains appeared to be immunologically identical.

The observations reported are of definite interest and value concerning what, for a time, proved a vague and puzzling problem.

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—*R. A. K.*

Postgraduate Courses, Delivered in the English Language in the Leading Hospitals of Paris (France), During the Summer of 1931

The Faculty of Medicine of Paris (The Medical School of the University) announces that, during June and July, 1931, a comprehensive series of postgraduate courses will be presented. The enterprise is conducted under the auspices of the Association for the Development of Medical Relations (the "A.D.R.M."), a commission sponsored by the French Government.

The work will be presented in the English language. Clinics, lectures and demonstrations will be conducted in the great hospitals of Paris, on a wide variety of topics, by the most eminent French clinicians. A nominal fee will be charged for each course. Upon the completion of each course, the student who qualifies will receive a certificate covering the work, signed by the professor in charge.

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